KNOWLEDGE SYNTHESIS IN THE BIOMEDICAL LITERATURE:

NORDIHYDROGUAIARETIC ACID AND BREAST CANCER

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This dissertation refines knowledge synthesis from publicly accessible databases, based on the model of D.R. Swanson. Knowledge synthesis endeavors bring together two or more non-interactive literatures to create combinatorial research data on a specific topic. In this endeavor the biomedical literature was searched on the anti-neoplastic agent nordihydroguaiaretic acid (NDGA) for its potential role as a functional food in the chemoprevention of breast cancer. Bibliometric cocitation was utilized to identify complementary but non-interactive literatures in the disciplines of biomedicine and dietary science.

The continuing specialization and fragmentation of the cancer literature degenerates the potential usefulness of cross-disciplinary research and information. As the biomedical sciences become more specialized the potential increases for isolation of discoveries and for failures to connect science to the needs of the people. Within the information science discipline several techniques are available to bridge the isolation between discoveries recorded in different sets of literatures. Electronic database searching with combinatorial keyword entries, syllogistic modeling and bibliometric author cocitation analysis are the principle techniques applied in this endeavor.

The research questions are addressed to the absence or presence of human *in vivo* research on breast cancer with the potentially chemopreventative functional food NDGA. Utilizing a syllogistic model the literatures of functional foods, nordihydroguaiaretic acid and breast cancer were searched with designated combinatorial keywords. The documents retrieved were subjected to author cocitation analysis to demonstrate disjointness or connectivity of the two

complementary literatures. The results demonstrated a possible preventative relationship between breast cancer in women and nordihydroguaiaretic acid, a phytochemical antioxidant and potential functional food. The results of the study are consistent with D.R. Swanson's pioneering work in knowledge synthesis. Swanson's methods can be used to identify non-interactive, disjoint literatures. Continuing support for his techniques has been demonstrated.

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INTRODUCTION

Overview

This study replicated the knowledge synthesis model of D. R. Swanson, on the literature related to nutritional implications in breast cancer and the literature of a possible therapy, nordihydroguaiaretic acid. Knowledge synthesis brings together two or more non-interactive literatures to create combinatorial research data on a specific topic. Bibliometric cocitation was utilized to identify complementary but non-interactive literatures in the disciplines of biomedicine and dietary science.

Nordihydroguaiaretic acid (NDGA) is a naturally occurring phytochemical extracted from the plants *Larrea divaricata* and *Larrea tridentata.* Nordihydroguaiaretic acid is an antioxidant, with antitumorgenic and anticarcinogenic properties. It has been extensively analyzed and is utilized as a prototype antioxidant for *in vitro* research on biological systems. Relevant *in vitro* research has been conducted on molecular and cellular mammary gland materials, both animal and human (Reddy, Everhart, Eling & Glasgow, 1997; Palmantier, Roberts, Glasgow, Eling & Olden, 1996; Earashi, Noguchi & Tanaka, 1996; Noguchi, Rose, Earashi & Miyazaki, 1995). Experimental *in vivo* research has been conducted on laboratory animals with induced or spontaneous mammary tumors (McCormick & Spicer, 1987; Rillema, 1984). Reports of scientific studies undertaken to test NDGA in human subjects are rare. One rarity occurred in 1970, following a scientific paper presentation at the University of Utah. In 1969 the report of a dramatic regression of melanoma in a patient taking "Chaparrel Tea" the major chemical ingredient being NDGA, spurred this effort. The study involved 59 patients with various types of tumors. It was basically a test of "Chaparrel Tea" which had consistently been reported in non-scientific literature as having

antitumorgenic properties. “Four patients had significant tumor regressions…The majority of patients, 27, had subjective improvement while many of their tumors were objectively growing rapidly.” (Smart, Hogle, Vogle, Broom & Bartholomew, 1970, p. 43). This study by a group of practicing physicians has since been surpassed for scientific accuracy and investigative detail. Reports from the field of dermatology attest to the antiproliferative effects of externally applied preparations of nordihydroguaiaretic acid, usually referred to as ‘masoprocol’ (m-nordihydro-guaiaretic acid) (Olsen, Abernathy, Kulp-Shorten, 1991; Barnaby, Styles & Cockrell, 1997). Other *in vitro* studies on mice, which were conducted by the National Cancer Institute in 1955, on Sarcoma 180 did not demonstrate an inhibitor effect of NDGA (Stock, Clarke, Philips, & Barclay, 1955). However, these studies were quite crude, i.e., visual inspection of reduced tumor size with empirical dosing; no cellular or biological examination of the tissues was performed.

NDGA has a long history of commercial use as a food preservative and materials stabilizer. The connection of NDGA and breast cancer prevention therapy lies in the current intense pursuit for a ubiquitous, nongenetic cause for a high percentage of human breast cancer (Ardestani, Ahadian, & Watson, 1996). The prevention of cellular development of human breast cancer probably lies in antioxidant nutrients and so-called “functional foods”. Functional foods are those foods, which contain specific components with demonstrated anticarcinogenic effects in experimental systems (Williams & Wynder, 1996). An extensive listing of functional foods, i.e., food-borne inhibitors of experimental cancer are found in Appendix A (Hasler, 1998;Williams & Wynder, 1996; Bailey & Williams, 1993). Functional foods are primarily found in plants, therefore are commonly phytonutrients or phytochemicals. In this study a logical connection for use of the phytochemical NDGA as a functional food additive (or “nutraceutical”) and chemopreventative agent for breast cancer was studied.

The incidence of breast cancer in females is second only to lung cancer in the United States (U.S.). Worldwide, breast cancer in women contributes 21% to the global burden of disease from cancer, with over 300,000 deaths attributed to breast cancer (Parkin, 1999; Pisani, 1999; Ferlay, 2001). Statistics on breast cancer are reported in concert with pathological classifications, as invasive breast cancer, in situ breast cancer, and lobular carcinoma in situ. In the U.S., from 1940 to 1988, a steady increase was seen in the incidence of invasive breast cancer; between 1988 and 1996, incidence rates of invasive breast cancer in the U.S. have been approximately level (American Cancer Society, 1999). However, incidence rates of in situ breast cancer have increased considerably over the past 25 years, primarily due to an increase in ductal carcinoma in situ (DCIS). The less common lobular carcinoma in situ (LDIS) incidence rates have remained level since 1988. This brief background information on breast cancer indicates a losing battle; detection and treatment have not slowed the incidence of breast cancer. Now is the time to closely examine the alternative of primary prevention.

Purpose of the Study

The purpose of this study was to investigate whether there is a content relationship between the two complementary literatures of functional foods and nordihydroguaiaretic acid, and the literature of breast cancer, or conversely, to establish the sets of literatures as non-interactive or disjoint. A knowledge synthesis methodology was utilized in this study. The intent was to identify a possible chemopreventative for breast cancer. The knowledge synthesis methodology identifies two sets of biomedical research literatures that share content-focus and information, i.e., are complementary, but do not site each other and are not co-cited and therefore not linked by discovery. The technique as developed by D.R. Swanson in his seven examples of literature-based knowledge synthesis endeavors was replicated (Swanson, 1996). The paradigmatic scheme

of complementary but disjoint literatures as researched in this study is depicted in Appendix B. The literatures of nutritional science, biomedicine and breast cancer as used in this study require some definition of terms.

The following definitions of terms are from the *On-Line Medical Dictionary©*, a medical dictionary, (©CancerWEB 1997-2003, CancerWEB Project, Academic Medical, Publishing, U.K., http://cancerweb.ncl.ac.uk/omd/), (1997-2003), the Merriam-Webster's Nineth New Collegiate Dictionary (1991) and various cited references as indicated.

1. Antioxidant: a substance that inhibits oxidation or reactions promoted by oxygen or peroxides (Merriam-Webster's Nineth New Collegiate Dictionary, 1991); any substance that prevents or reduces damage caused by reaction oxygen species (ROS) or reactive nitrogen species (RNS). ROS and RNS are highly reactive chemicals that attack other molecules and modify their chemical structure (Awasthi, Singhal & Awasthi, 1996); synthetic or natural substances added to products to prevent or delay their deterioration by action of oxygen in air. In biochemistry and medicine, antioxidants are enzymes or other organic substances, such as vitamin E or beta-carotene, that are capable of counteracting the damaging effects of oxidation in animal tissue (On-Line Medical Dictionary, 1997-2003).
2. Antitumorigenic: substance or agent capable of preventing tumor formation; substance may affect cells directly to prevent tumor formation, or affect transformed cells themselves, i.e., formed tumor cells (VERIS, 1999).
3. Carcinogenesis: process of cancer formation; the generation of cancer from normal cells.
4. Carcinogens: substances that increase the risk of neoplasms in humans or animals. Both genotoxic chemicals, which affect DNA directly, and nongenotoxic chemicals, which

induce neoplasms by other mechanisms, are included (On-Line Medical Dictionary, 1997-2003).

5. Chemopreventative agent: nutritive or nonnutritive food component, phytochemical or zoochemical being scientifically investigated (or purposed as a candidate for investigation) as a potential inhibitor of carcinogenesis for primary and secondary cancer prevention (Greenwald, 1999).
6. Functional foods: any modified, enhanced, or enriched food ingredient or food additive that may provide a health benefit beyond the traditional nutrients it contains(Milner, 2000); foods containing components that have demonstrated anticarcinogenic effects in experimental systems (Williams & Wynder, 1996);
7. Nordihydroguaiaretic acid (NDGA): a naturally-occurring phytochemical lignan extracted from the creosote bush, i.e., *Larrea tridentata* Cov.; also produced synthetically; known properties include: phenolic antioxidant, lipoxygenase inhibitor, arachidonic acid inhibitor, antitumorgenic and anticarcinogenic. [history of use as food preservative, antioxidant].
8. Phytochemicals: biochemicals derived from naturally-occurring plant sources, and may be beneficial for health or treatment of disease (Croteau, Kutchan & Lewis, 2000);
9. Undiscovered connections: parallel occurrence of discipline-specific discoveries or disclosures, in two scientific fields, which are mutually unknown to each other; the existence of 'undiscovered connections' in scientific literature is the providence of knowledge synthesis endeavors, which strive to connect two or more important, isolated events, informational documents, discoveries, and/or research conclusions (Swanson, 1986a).

Statement of the Problem

The continuing specialization and fragmentation of the cancer literature degenerates the potential usefulness of cross-disciplinary research and information. As the biomedical sciences become more specialized and more intense, the potential for isolation of discoveries and failure to connect science to the needs of people becomes more probable. The cause of this isolation may occur in two major ways: (1) discoveries in highly specialized areas such as breast cancer, which have immense potential and applicability may be unnoticed by others for significant periods of time; (2) the intense competition between researchers and research entities. Fewer researchers are working in the application areas such as with NDGA, where less funding is available, and these less prestigious efforts go unnoticed. There is a lack of systematic knowledge synthesis of the breast cancer literature and the NDGA literature. The technique of knowledge synthesis proposed in this study formed a bridge between these two complementary but non-interactive literatures.

Significance of the Study

Several prominent examples are available of isolation of discoveries in the biomedical and scientific literature. The first type of isolation involving discoveries in highly specialized fields is attested to in the work of D. R. Swanson. His research in connecting non-interactive biomedical literatures on dietary fish oil and Raynaud's syndrome treatment (1986b), migraine and magnesium levels (1988), and somatomedin C, arginine, wound healing and aging (1990a) demonstrates the occurrence of three incidents of the first type of isolation. The second type of isolation involving intense competition is prominently evident in the Human Genome Project and related entities. Progress in gene identification and isolation has out-distanced development of therapies or preventative measures for the identified genetically related diseases and disorders

(Cattaneo, E., Rigamonti, D., & Zuccato, C., 2002). Thus, the aftermath of isolation of information in specialty areas surrounding biomedicine needs to be stressed on several fronts. It was anticipated that this study, as one front, would be able to demonstrate a relationship between breast cancer and the use of NDGA as a chemopreventative, and would foster further studies that could ultimately lead to a prevention and therapy for breast cancer.

Epistemological Basis

When approaching the process of knowledge synthesis, the point of beginning is examination of information. Information is the 'phenomenon' of interest in this research. Within the discipline of information science, techniques of information retrieval, information usage, and information counts have been studied for many years. Moreover, studies which relate the 'phenomenon' of information to the study of information science have been described in the literature but have largely been found wanting in theory. Bertram Brooke's "metrical space" of information (1980) places the phenomenon of information into an ontological scheme first described by Karl Popper. Brookes' begins with an analysis of Karl Popper's scheme of three worlds and develops a reasoned critique as to why information science must move toward a new, qualitative analytic technique if we are to capture the real meaning of information measurement. His theory development attempts to capture the subjective 'world 2', of human knowledge or mental states. This theory is a starting point for examining knowledge synthesis as it bridges the 'world' of subjective knowledge and the 'world 3' of objective knowledge. Knowledge synthesis is about relationships: relationships between two literatures, two scientific specialties. And relationships are not totally objectified; they are without physical representation, thus are excluded from the physical 'world 1', yet their component parts are not totally subjective either.

When information is viewed as a phenomenon, a new context is developed. Information has an intrinsic, inherent essence that constitutes its existence as a phenomenon. Information *is* a string of data chips, and a document, and a still-life movie clip, and it *is* more. Information exists as the sum-total of the attributes of an object, indestructible, immutable, and ageless. In the study of information as a phenomenon, dissenting opinions are important to consider. Cross-disciplinary research and discourse about information has occurred in the following fields: (1) in physics, as the 'information paradox'; (2) in linguistics, as 'the generative grammar'; and (3) in mathematics as 'entropy'.

Information as a phenomenon is described, researched and hypothesized about in the field of physics. Physicists' Leonard Susskind, Stephen Hawking, Roger Penrose conduct research in the futurist field of a quantum theory of gravity (Susskind, 1997; Hawking, & Penrose, 1996). They debate the merits of 'black holes' and their contribution to the possible loss of information. The discourse seems to be that a 'black hole' may be the sum-total of a mechanism for alienation of matter, inclusive of information about that very matter (Hawking & Penrose, 1996), or, if the laws of nature are symmetric, information is only scrambled and is retrieval by microreversibility. The question of what happens to information in matter 'destroyed' by a black hole when the hole evaporates is called the information paradox (Susskind, 1997). An answer to the information paradox has momentous implications for information science and knowledge synthesis.

The disciplines of communication and language share many constructs with information science. In the field of linguistics, Noam Chomsky's proposal of a generative grammar was a radical departure from the thinking of the 1950's. Campbell, writing in Grammatical Man (1982), juxtaposed the acquisition of language development (as hypothesized by Chomsky) with

the evolution of living organisms. The centrally shared component was described as "inventiveness," a shared, internal, generative principle or rule that can mutate (Campbell, 1982, p. 95-97). In 1998, a large stride was taken in proving Chomsky's hypothesis was correct when research on an extended family gave a genetic clue to language. In February 1998, geneticists "found on chromosome 7 a distinctive stretch of DNA that contains about 100 genes, one of which appears to cause a severe speech and language disorder in nearly half the members of an extended English family" (Bower, 1998, p. 71). When the genes for language are explicated, one of the highest order cognitive functions can be understood.

The concept of entropy is a familiar one in information science. Claude Shannon's (1948) theorems on information entropy, which explored the theoretical base of information transmission and stability, have served as the basis for movements to quantify information and to explain information as a phenomenon.

The processing of information, as a phenomenon and as a construct is another arm of knowledge synthesis. Bibliometric analysis of the literature of a field is a method of processing information contained in formal, text-based documents. Bibliometric analysis is the paramount process by which connections and linkages can be made.

Bibliometric database analysis provides the repeatable, researchable, grounding of previously processed information. This information can be explicated as (1) author cocitation, and/or (2) most frequently cited author in a field or discipline. Bibliometric techniques can be utilized to identify the most prolific authors in a knowledge domain, and differentiate these author/scientists as working in the mainstream of a field, as tangential, or cross disciplinary. Examination of their works will reveal the concepts and theories that they pursue, and further analysis can relate the

occurrence of major events with a particular line of research, field exploration or discourse in a different field of endeavor.

Research Questions

The generic research question is: "Can solutions to problems in one discipline be found in the literature of another discipline by finding unrecognized links between the literatures of the two disciplines?" This study asks the specific question: "Does there exist a possible preventative relationship between breast cancer, and nordihydroguaiaretic acid (NDGA) a phytochemical antioxidant?" The following research questions were addressed via replication of the knowledge synthesis model of D. R. Swanson:

The specific research questions in the study are as follows:

1. Will cocitation analysis of the public literature on functional foods and nordihydroguaiaretic acid, exclusive of the breast cancer literature, reveal undiscovered connections?
2. Will cocitation analysis of the public literature on functional foods and nordihydroguaiaretic acid, exclusive of the breast cancer literature, reveal linkages of a possible preventative agent?
3. Will cocitation analysis of the public literature on nordihydroguaiaretic acid and the public literature on breast cancer, reveal undiscovered connections?
4. Will cocitation analysis of the public literature on nordihydroguaiaretic acid and the public literature on breast cancer, reveal linkages of a possible preventative agent?
5. Will cocitation analysis of the public literature on functional foods and nordihydroguaiaretic acid and the public literature on breast cancer, reveal undiscovered connections?

6. Will cocitation analysis of the public literature on functional foods and nordihydroguaiaretic acid and the public literature on breast cancer, reveal linkages of a possible preventative agent?

A syllogistic paradigm has been constructed to illustrate the logic of knowledge synthesis in the literature search process:

A = Functional foods literature [as nutritional anticarcinogens].

B = NDGA literature [as an antioxidant and anticarcinogenic agent].

C =Breast cancer literature [prevention of].

thus:

A relates to/effects B = AB. In other words: $A \cap B$.

B relates to/effects C = BC. In other words: $B \cap C$.

if A relates to B, and AB effects C = (A intersection B) intersection C = ABC. In other words: $(A \cap B) \cap C$.

Stated as formal hypotheses, the research questions are as follows:

H_1: In the syllogistic paradigm of A intersection B, a literature search of the animal and human cell research conducted with nordihydroguaiaretic acid will establish properties of nordihydroguaiaretic acid shared with functional foods.

H_2: In the syllogistic paradigm of B intersection C, cocitation analysis of the NDGA *in vivo* research literature and breast cancer literature will reveal an absence of linkage, therefore disjointness of the literatures.

H_3: In the syllogistic paradigm of A intersection B intersection C, an undiscovered public knowledge phenomena will be explicated, i.e., nordihydroguaiaretic acid is chemopreventative for breast cancer.

Assumptions and Limitations

The assumptions and limitations addressed here cover the wider scope of experimental research, which is the anticipated benefactor of knowledge synthesis endeavors. The assumptions are:

1. In human cancer, the identification of a suppressing agent, or preventative, holds more promise than the search for a blocking agent. The agents that initiate human cancer are numerous, and as yet mainly unidentified. Exceptions are tobacco and aflatoxin BI (AFBI), which are classified as carcinogens. The task of proving initiating agents and identifying blocking agents is more formidable.
2. A holistic, environmentally focused approach to disease prevention has precedent over disease treatment and premature death from breast cancer.
3. Thirty five to fifty percent (35 to 50%) of cancers are food related (Williams & Wynder, 1996; Bailey & Williams, 1993)
4. Sufficient literature connections can be made to establish nordihydroguaiaretic acid as a type of functional food additive.

The limitations are:

1. Epidemiological data provides associative connections, but does not establish causality. Compensatory metabolic changes that may occur with dietary changes may not be identifiable (Hasler, 1998).
2. Establishing the authenticity of preventative measures or therapies is problematic, particularly in breast cancer when the disease process is multifaceted and causality is multifactorial. The lack of surrogate markers of disease development is another complicating factor
3. The complexity of the food substances consumed complicates the establishment of a strong scientific base.
4. The use of food additives as chemopreventative mechanisms is a newly heralded concept.

5. The complete scientific analysis of plant phenols with antioxidant activity may not be available, and the analysis of antioxidant activity may not explain the complete role of NDGA as an anticarcinogenic agent.
6. The literature searches are limited to the years 1980 through May 2002.

CHAPTER II

REVIEW OF LITERATURE

The ever increasing bodies of knowledge and information in multiple fields of study, the problem of authentication of electronic data; the complexity of searching for relevant information or literature; and the yet unexplicated tasks and techniques for determination of cross-over in domains of knowledge has become one of the challenges for the knowledge worker. Information and knowledge for decision making, for application to practice, and for changes in protocols have become preeminent problems for the researcher, the academician, the healthcare professional, and the business executive. "Information synthesis is one of the most valuable contributions a scientist can make." (Goldschmidt, 1986, p.215). Knowledge synthesis is one process outcome to make order out of chaos. In the timely article "Back from Chaos" (1998b), Edward O. Wilson presents the unification of knowledge as the structural change required to understand the human condition. Consilience of thought across disciplines, across knowledge domains, and across the branches of learning would bring order out of chaos (Wilson, 1998a).

The model of knowledge synthesis proffered by D.R. Swanson is based on the underlying premise of knowledge discovery through examination of (1) the bibliographic record of biomedical and scientific literatures, and (2) the subsequent ability to establish a set of non-interactive, but complementary literatures related to a novel hypothesis of interest. In 1986 D. R. Swanson coined the term "undiscovered public knowledge" (1986a, pg. 103) to address the incompleteness of search and retrieval methods in the medical field, and the resultant collection of undiscovered knowledge. Public knowledge, as defined by D.R. Swanson, is the information published in openly available documents, which the 'public' may access at will. Due to the

volume of documents and the specialized study paths of scientists, little if any of the individual authors makes any disciplinary crossover. Therefore the potential exists for important and vital knowledge to remain 'undiscovered' and linkages to remain hidden.

The process of knowledge synthesis as developed by D.R. Swanson is highly likely to culminate in a new relationship, because of two characteristics of biomedical and scientific literature. These characteristics are: (1) the narrowly focused nature of disciplines conducting scientific inquiry; and (2) the descriptive nature of the titles of biomedical and scientific literature. The narrowly focused natures of scientific inquiry results in journals that specialize in one narrow topic and in which the collegial groups publish, cite, and co-cite each other's works. Henry Small, in 1973 proposed a knowledge structure of the scientific literature based on cocitation analysis. He theorized that the context in which a scientific cocitation occurs demonstrates subject similarity and association or co-occurrence of ideas (Small, 1973). Then Swanson, writing on "Intervening in the Life Cycles of Scientific Knowledge" (1993), extended this idea to portray knowledge synthesis as the link between scientific knowledge life cycles and bibliometrics. The second consistent characteristic of biomedical and scientific literature, e.g., the titles of journal articles, make them prime candidates for cocitation analysis. The titles of biomedical and scientific journal articles are descriptive of the subject matter and content, plus they often identify the purpose of the publication, i.e., review, report of experimental results, report of unusual findings, or continuing analysis in an area.

Another more practical application of a knowledge synthesis structure is found in the everyday practice of clinical medicine. As more scientific information and research results become available via electronic media, pressure and onus develop on the clinicians and practitioners of clinical medicine to utilize this information immediately. A prominent focus in

the present climate is to incorporate *evidence-based medicine* at the primary care level. In order for evidence-based medicine to continue its required, rapid development and renewal of information, an information synthesis methodology is necessary.

Knowledge Synthesis

The quintessential search for knowledge has lead scholars, researchers, academicians, and scientists down many and varied paths. The search has been very successful, hence the doubling of retrievable knowledge every two years. Collectively human society has amassed more information than is possible for an individual to recognize and assimilate. Computerized algorithmic searches can retrieve thousand-plus volumes of data and information from a single "keyword," yet not achieve the objective of the searcher. This is not due to an absence of techniques for searching or a paucity of software to retrieve data; rather, it is a result of the need for methods designed to fully utilize the capabilities of search engines, artificial intelligence/agency, and protocols. One such method may be the structured, directive process of knowledge synthesis. Knowledge synthesis is one way to address the information isolation problem.

Knowledge synthesis is a process, which results in a composition, a composition produced by the discovery and merging of attributes of objects, cognitive pieces, and esthetic experiences. And information is the player...the instrument of violin and brass. Knowledge synthesis across disciplines is a process of unification, a consilient endeavor that should be employed in the academic and research worlds. It is the means by which presentations can be prepared to inform audiences, the means by which the scientist can decide to test a particular hypothesis. This research approaches the endeavor of developing a method of knowledge synthesis by utilizing

the techniques of bibliometrics and structured literature searches, to accelerate and enhance knowledge synthesis in the biological, biomedical and dietary sciences.

Knowledge synthesis as addressed in this research includes as its domain the universe of scientific knowledge and is conducted for the purpose of deriving novel inferences between disjoint but complementary literatures. The scope of the research is the biomedical and scientific literature as bibliographically displayed via electronic databases that are relevant to mammalian physiology. The search for undiscovered connections is the main feature of the process. When successful, the results may provide resolution of disjointness, i.e., clarification of a problem, or a combinatorial process, or description of a causal mechanism (Swanson, 1991). This paradigmatic scheme of complementary but disjoint structures within the literature of science is displayed in Appendix B.

The approach to knowledge synthesis as developed by Swanson has been studied by other researchers and extended by one group. Michael Gordon and Robert Lindsay (1996) replicated Swanson's findings on Raynaud's and fish oil, using computer software to generate record counts and statistical methods to find topics connected to the source literature. They then computed the relative frequency of terms from disjoint but related literatures, and identified the target literature. Again, in 1999, Lindsay and Gordon report on experiments with lexical statistics utilized in attempts to extend the work of Swanson. They report on the use of relative frequencies of words to discover an intermediate literature, in the fashion of Swanson and his discovery of unknown connections between migraine headaches and magnesium. Their research was contrary to their hypothesis but consistent with Swanson's observation (1999, pg. 583).

Work of D.R. Swanson

The methods for knowledge synthesis developed by D.R. Swanson were utilized in this research. Swanson examined specialized biomedical literatures that were non-interactive (or disjoint), but when the arguments presented in each body of literature were combined, new inferences and conclusions were drawn. “Non-interactive” or “disjoint” literatures are defined as two literatures that have no cocitation and no citing of each other. The use of citations and referencing others works is a time-honored method of communication in scientific and scholarly works, and provides the linkages for more discoveries (Small, 1973; Davies, R., 1989; Davies, R. 1990; Roberts, D., 1990). However, with the increasing amounts of knowledge and the more specialized fields of inquiry, important connections and linkages in the literature via citations may not be as comprehensive as needed. Therefore, this dissertation is a further attempt to provide the foundation for a literature-based approach to scientific discovery. Other terminology for this process is knowledge synthesis or knowledge discovery.

D.R. Swanson developed a logical argument approach to examining the content of non-interactive biomedical literatures deemed to have undiscovered connections or linkages. The result of the connections or linkages consequently became a new discovery, which added significantly to knowledge of disease treatment and understanding of the pathophysiology of disease. Swanson’s model began with a problem, or the idea of a relationship, a possible ‘cause and effect’, or a search for a cure. This heuristic approach to problem solving is replete in the history of discovery. D.R. Swanson began each research endeavor with an extensive review of the biomedical literature, primarily MEDLINE® (MEDLINE: Medical Literature, Analysis and Retrieval System Online), an online database (® National Library of Medicine, Rockville Pike, Bethesda, MD, www.nlm.nih.gov), via Dialog® (Dialog), an online-based information services

company (® The Thomson Corporation, Cary, NC, www.dialog.com/) (1986a; 1986b; 1987;), Excerpta Medica via Embase® (EMBASE), a human medicine and related disciplines database (® Elsevier Science, B.V., New York, NY) (1986a; 1986b;), and Dialog SciSearch ® (SciSearch), a cited reference science database (® Institute for Scientific Information [ISI®], Thomson Scientific, Philadelphia, PA), (1986a). He then developed a syllogistic argument to focus the primary elements. Early research (1986a; 1986b) provided evidence of undiscovered causes or cures for disease related to non-interactive biomedical literature. As his research fields became more refined, he expanded his techniques to accommodate variations in the literature presentations thus broadening application of the syllogistic approach (Swanson, 1989). Three distinct phases of discovery and syllogistic development are found in the major research he has reported. These three phases, by date of occurrence, will be briefly discussed in the following format:

- Idea or problem to be researched;
- Syllogism structure (the syllogism structure is not prepositional logic, but rather a paradigm to enhance understanding);
- Literature search results;
- Conclusions.

Phase 1**:** In the *Library Quarterly*, April 1986a, Swanson developed a theme of undiscovered public knowledge and discussed the deficiencies in information retrieval processes. He used as example the non-interactive literature on the ability of fish oil to improve the symptoms of Raynaud's disease, a vascular occlusion condition which can lead to severe pain and potentially amputation of fingers, toes, earlobes. The following two hypotheses and the conclusion, in the form of a syllogism, were constructed:

H_1 = A = undiscovered cause or cure;
H_2 = B = intermediate link;

Conclusion = C = known literature re: problem or disease.

In this research example:

A = fish oil with eiscosapentaenoic acid;
B = reduction of platelet aggregability and blood viscosity;
C = improvement in Raynauds' disease.

hence:

- A causes B = AB;
- B influences/causes C = BC;

therefore:

- A causes/leads to/implies C = AC.

In this research exploration, D.R. Swanson started with data describing the attributes of fish oil on the vasculature and vascular components of humans, and with a concurrent search of the phenomenology of Raynaud's disease. He provided a more in-depth analysis and explanation of this process in later articles, i.e., *Perspectives in Biology and Medicine,* (1986b), and *Journal of the American Society for Information Science*, (1987). He speculates on the temporal development of literature, and suggests that it must reach a critical mass and have an unintended logical connection between two disparate literatures before co-citing will occur. In a concerted effort to demonstrate the reality of non-interactive literatures, he selected a 59-item bibliography of fish oil and Raynaud's literature, for the purpose of discerning a connection in a carefully selected bibliography (1987). He subjected the literature items to a descriptor study, comparing and sorting the medical subject heading (MeSH). Then, he continued with a bibliographic coupling study, a cocitation study and mutual citation analysis. The results did not yield clues or bibliographic connections between these two logically connected bodies of literature. Thus D.R. Swanson was able to claim discovery of a new, previously unknown potential cure or treatment for Raynaud's disease.

While D.R. Swanson did not describe any systematic process for discovering the connections between fish oil and Raynaud's disease treatment, he suggested some procedural steps, which are to be incorporated in the current research. They are as follows:

Start with a search for answers to an authentic problem;
Look in the literature, not in the laboratory;
Read extensively and continue a problem-oriented trial-and-error process of exploratory database searching;
Collect articles indexed with both hypotheses;
Use techniques to *exclude* connections in the literature, i.e., look for the absence of retrieval clues.

Phase 2**:** In D.R. Swanson's second research on logically related non-interactive medical literatures, he started with a set of known literature on migraine headache, as the "C" of the syllogistic paradigm, and began a search for intermediate links in the causal chain of the disease process. Utilizing the search parameters available in MEDLINE files, he scanned subgroups of article titles on migraine, and began a process of surmising and conjecturing to discover possible links, therapies, or cures that had not been previously connected. Working from the premise of a 'deficiency' as a potential link, he conducted MEDLINE set-intersections for the thousands of records retrieved on migraine and magnesium (magnesium being the conjectured deficiency). This technique yielded sufficient information to direct pursuit of other related linkages. The next steps were an in-depth searching, and reading of the two sets of literature, and the establishment of a logical, biomedical connection between the two literatures. The process at this point has established the syllogism below:

- A = conjecture or hypothesis, yet unknown, related to magnesium deficiency as causal factor;
- B = intermediate literature, on previous explanations for causes of migraine;
- C = literature on migraine headache.

Analysis of the literatures identified 11 linkages relevant to both migraine pathophysiology and the pathophysiological effects of magnesium deficiency. Dr. Swanson also discovered one article

which had previously made a connection between migraine and magnesium deficiency, and which has unusual standing as almost a bridge between two otherwise non-interactive literatures (1988). According to Swanson (1988) a 1985 paper by Burton Altura alludes to some of the eleven connections but makes only sparse reference to the migraine literature. The Altura paper appeared to have been ignored or overlooked, as its had not been cited by anyone else as of 1987.

He followed with a cocitation analysis on Dialog SciSearch, which confirmed, "the migraine and magnesium literatures were communicative clusters within themselves but were in effect mutually non-interactive." (pg. 548, 1988). He relates the significance of this study to the form of its argument and the citation structure of the literature on which the argument is based. Exploration and extraction from the two literatures yielded new conclusions and connections, not in a predictive manner, but rather in a *retro*dictive way (pg. 34, 1990a). This second phase differs from Phase I in the starting point of the search, the syllogistic structure, and the final analysis. Emphasis in the exploratory process stresses the discarding of hypotheses already supported by intersecting literature. This process consists of an "AC intersection search" as one method of discarding conjectures of no interest. In areas of biomedical interest, a MEDLINE trial search of the "A" literature is run, to discover if any articles are found in common with "C" literature; if no articles, a "negative test" results and the exploration proceeds (Swanson, 1990a).

Phase 3: The third knowledge discovery process D.R. Swanson reports, relates to the roles of dietary arginine (an amino acid) on somatomedin, a growth stimulant, and their effect on nutrition repletion in cases of malnutrition, AIDS (acquired immunodeficiency syndrome), wound healing, chronic illness and anorexia (Swanson, 1990b). The phase 3 exploratory study uses an alternate pattern, or exception, to the previous syllogistic paradigms. The two premises and the conclusion are all known sets of literature, but no combinatorial studies had been done or

explicit links established between the sets of literature. “A” and “B” are non-interactive sets of literature, thus “AB” have an unknown implicit connection, and “B” mediates the effect of “A” on “C”. The structure is as follows:

- A = known literature on dietary arginine;
- B = known literature on somatomedin;
- C = known literature on nutrition repletion, but with no combinatorial studies with A or B.

Therefore:

- AC = known;
- BC = known;
- AB = unknown, implicit connection.

In this literature-based approach to scientific discovery, D.R. Swanson, through a careful, systematic synthesis of the literature, makes five pair of astounding biophysiological connections that implicitly suggest that arginine intake might increase blood levels of somatomedin and lead to improvement from protein tissue wasting. If this connection leads to treatment in protein-calorie malnutrition, the impact will be substantial.

In subsequent studies, D.R. Swanson has continued to refine these search techniques and to broaden their applicability to information retrieval of non-interactive literatures (Swanson, 1989,1993; Swanson & Smalheiser, 1997). In the more recent publications he changes descriptive terms, i.e., ‘complementary’ to indicate logically connected biomedical literatures, and ‘disjoint’ to describe the non-interactive aspects of the literatures (Swanson, 1991; Swanson & Smalheiser, 1997). Additionally, he introduces a software package called ARROWSMITH. ARROWSMITH is described as “...embod[ing] a replicable database search procedure and related software that produces heuristic aids to finding complementary literatures and to derive novel scientific hypotheses.” (Swanson, 1997, pg. 201). A close examination of the article reveals the major use of ARROWSMITH is to derive a possible novel hypothesis by word

association counts, but the human researcher must then analyze these words (Swanson, 1996, 1999).

The essence of knowledge synthesis, as practiced by D.R. Swanson, begins with the 'search' for a novel hypothesis, via use of ARROWSMITH, or more heuristic methods such as personal interest in a subject matter, or concern for a cure or treatment for a disease state. The process or protocol for testing the hypothesis continues with (1) online searching of bibliographic scientific databases; (2) isolation of two literatures related to the hypothesis; (3) examination of the two literature structures to establish complementarity; and (4) ascertaining if the two literatures are disjoint, i.e., non-interactive by citation or cocitation (Swanson, 1979, 1994). The process will be replicated in this research study.

Bibliometrics

The bibliometrician is by feint the enabler in information science. Although abstract and disembodied by technique, as claimed by White and McCain (1989), bibliometrics nonetheless is grounded in human behavior. The individuals' choice of title, citation, co-author, and ultimately, discipline, are unique choices. The linguistic form, syntax, and sentence structure are likewise unique to the individual. An explanation of this argument becomes evident as one examines the breadth and depth of bibliometrics, beginning with the definitions presented by bibliometricians in their respective field of endeavor.

According to Paisley (1990) evidence of bibliometric techniques can be traced to the Talmudic scholars in the Middle Ages as they verified the accuracy of the multi-copied texts of Judaism. In the same context, Paisley's analysis of the phases of bibliometric research will form the structure of the following information.

First-Generation Bibliometric Research

Statistical analysis of the characteristics of text constitutes the bulk of the first-generation bibliometric research. The first generation includes the first bibliometricians (larger unnamed); however for purposes of definition, an acceptable time period can be identified from 1875 to mid-1940. Bibliometrics in this era was called *statistical bibliography* (Diodato, 1994), and a definition given by Pritchard (1969) states:

> "Statistical bibliography...shed[s] light on the process of written communication and of the nature and course of development of a discipline (in so far as is displayed through written communication) by means of counting and analyzing the various facets of written communication." (p. 348)

In this era the foundational bibliometric computations of Lotka (1926), Bradford (1934), and Zipf (1935) were published. The common referrals to these early bibliometricians and their work characterize their contributions as "laws"; this paper will remain consistent in this tradition. However, may it be noted, their work's were actually models of computations, which attempted to be explanatory, and did not have the predictive attribute of laws. Lotka examined publications in chemistry and physics for the late nineteenth and early twentieth centuries. According to Potter (1981) Lotka's law states there is an inverse relation between the number of documents produced and the number of authors producing them. Thus, Lotka's law suggests that a few authors account for a relatively large percentage of publications in a field, while many other authors produce only one or two publications each. Bradford, as explained by Drott (1981) examined bibliographies of applied geophysics and lubrication and found a few journals are clearly prolific, while most produce only one article. This pattern of dispersion is best known as 'core and scatter'. Zipf, working from a base of humanism, analyzed word frequency in human

speech and text as a measure of least effort (Wyllys, 1981). These quantitative, statistical analysis techniques formed the basic "laws" of bibliometrics, and exemplified the focus on characteristics of text rather than on the meaning of text.

Second-Generation Bibliometric Research

This period covers the field of bibliometrics from late 1940's through late 1980's. In the 1940's, linkage studies began to appear in bibliometrics. Citations from reference lists of scholarly papers begin to be analyzed for information about the intellectual network of scholars and their information environment. The second-generation bibliometric researchers first focused on the source of the citation, i.e., journal article, book, unpublished report, conference documents, then moved to linkage studies of journal-to-journal and author-to-author citations, and finally cocitation measures. The prominence of linkage studies was fueled by external factors. National governments were concerned that poor communication in the scientific world was undermining costly research projects and bibliometric methods could be utilized to measure the inefficiencies. A prominent example is the extensive work by Francis Narin in 1976, funded by the National Science Foundation, a tax-supported entity. Narin measured scientific activity using evaluative bibliometrics to analyze some 2000+/- publications and their citations. Collaborative efforts with several European countries were conducted by the Netherlands Centre for Science and Technology Studies (CWTS). This center conducts bibliometric studies of research and development in their countries (van der Wurff, 1997). Secondly, researchers in information science and policymakers wanted to 'make sense' of the enormous body of public knowledge.

As this paper is directed to information scientists, researchers and scholars, the most valuable information regarding bibliometrics may be the broader, less-specific definitions which convey a

message of the enormous power of bibliometrics in the current information era. The techniques to be utilized in this research include the use of citation, cocitation analysis, and scientific domain analysis. Documents will be retrieved from biomedical and scientific fields, epidemiology, nutrition and dietary science. Documents other than strictly journal articles, will be examined, as they occur in the databases included. The inclusion of documents such as abstracts and papers from meetings, patents, technical reports, editorials, conferences papers, reviews and books extends the techniques into the field of informetrical analyses. This is essential in order to discover and acquire the most current data set and to position science as one source of information, along with epidemiological, ecological, and human environmental input. The electronic databases are limited by the quality of their indexing practices and their retrieval capabilities (Davies, 1990). Not withstanding this limitation it is highly likely we will find specialization has inadvertently but inexplicably slowed progress in the biomedical and biopharmacological sciences.

Description and History of NDGA

The subject of this dissertation is the potential use of the naturally occurring antioxidant *nordihydroguaiaretic acid* (NDGA) as a chemopreventative and anticarcinogenic agent for breast cancer. Interest in this subject has developed over several years. Breast cancer surveillance data and practice information have demonstrated a continually increased incidence of breast cancer, as well as a perceived change in morbidity. An accompanying interest in alternative medicine, particularly herbal medicinal pharmacology led to the first connections between cancer and nordihydroguaiaretic acid. In the initial stages of research, a number of agricultural, federal government and alternative medicine on-line databases were explored via the World Wide Web (WWW). Information gleaned from searches of the following online databases will be discussed.

1. Alternative Medicine:
    - Cyberbotanica, Plants and Cancer Treatments
    - Alternative & Complementary Medicine Center
    - The Alternative Medicine Homepage
    - Smart Basics, Nutrition for the New Millennium
    - HealthWorld Online
    - National Institutes of Health (NIH), National Center for Complementary and Alternative Medicine (NCCAM)
2. National Agricultural Library (NAL):
    - International Bibliographic Information on Dietary Supplements (IBIDS)
    - Integrated System for Information Services (ISIS)
    - Office of Dietary Supplements (ODS)
    - Food and Nutrition Information Center (FNIC)
    - Phytochemical Database, Agriculture Genome Information System (AGIS)
3. United State Department of Agriculture (USDA):
    - National Resources Conservation Service, National PLANT Database (PLANTS)
4. United States Food and Drug Administration (FDA):
    - "Everything" Added to Food in the United States (EAFUS)
5. Botanical Dermatology Database (BoDD)
5. United States Patent Office Database
6. United States Code of Federal Regulations Database

Alternative medicine online sites, inclusive of herbal products sites, were browsed in the beginning to collect background data on the clinical and consumer view of NDGA. A valuable clue was discovered which lead to the National Agriculture Library and federal government food additives and preservatives databases. In the 1950's and 1960's, NDGA was used in the United States as a food preservative for fats, lard, and other products. Studies had shown NDGA to be a relatively nontoxic food antioxidant and it was patented a number of times in the 1940's (Grisvold 1945, 1947a, 1947b, 1948; Adams, 1947; Shipner, 1945). Oliveto (1972) and Cranston, Jensen, Moren, Brey, Bell & Bieter (1947) have shown NDGA to be nontoxic and have no ill effects in acute studies on rats and mice. However other studies in which rats were fed amounts up to three (3) percent of their diet (Grice, Becking & Goodman, 1968; Goodman, Grice, Becking & Salem, 1970) showed development of kidney cysts. Based on these studies, in 1968 NDGA was removed from the list of approved antioxidants for use in food. It was placed

on the banned (BAN) list as a "substance banned prior to the Food Additives Amendment (FAA) because of toxicity", and on the illegal (ILL) list as "substances used or proposed for use as direct additives in foods without required clearance under the FAA. Their use is illegal." (FDA, Appendix A, Food Additives, pg.3, 1999). No attempts have been made to re-institute the use of NDGA based on the extensive research now available, which shows the multiple beneficial properties of the substance, including its anticarcinogenic effects.

The search for information on NDGA as a chemical product and its use as a food preservative, continued but with added difficulty. The older date and non-digitized state of the information hindered online searching. And, subsequent publications frequently state this information without any explanation or review of the studies to support the ban. It became necessary to correspond with the National Agricultural Library (NAL) via post mail when holding libraries refused to fill interlibrary loans requests. The following literature review comes from various sources and documents.

Nordihydroguaiaretic acid is a phytochemical lignan found in the creosote bush, *Larrea tridentata* Cov. and *Larrea divaricata* Cav., a common desert plant that covers a large area of the southwestern desert of the United States and northwestern Argentina (Anesini, Ferraro, Genaro, Cremaschi, Sterin-Borda & Borda, 1997). Varieties of the creosote bush grow throughout the Mojave, Sonoran, and Chihuahuan deserts, in the states of Texas, Arizona, Nevada, New Mexico, Utah and California, and in north-central Mexico (United States Department of Agriculture, IFSL, 1995). Creosote bush covers an estimated 35 to 46 million acres (Botkin, 1949; McAuliffe, 1994; United States Department of Agriculture, Natural Resources Conservation Service [USDA, NRCS], 1997). It also grows extensively in the Mexican desert and is considered native to Chile and Argentina. *Larrea divaricata* (synonym *Covillea*

tridentata) receives it common name, creosote bush, from a gummy secretion on the leaves that gives them a varnished look and imparts a distinctive creosote-like odour (Schmidt, BoDD [Botanical Dermatology Database], 1998). There is not complete agreement on the botanical classification of creosote bush, therefore alternative classifications are provided in Appendix C. The early agricultural research conducted by Botkin at the New Mexico College of Agriculture and Mechanic Arts (1949) identified the creosote bush in that area as *Larrea divaricata* Cav. Waller and Gisvold's work in 1945 on the phytochemical properties of creosote bush identified *Larrea divaricata* Cav. as the bush they studied. Likewise, other early investigators (Lieberman, Mueller & Stiller, 1947; Lauer, W.M., 1945; Perry, Kalnins, & Deitcher, 1972;) studied the properties of *Larrea divaricata.* However, in the more recent literature, researchers have listed *Larrea tridentata* Cov. as the source plant growing in the United States, and *Larrea divaricata* Cav. as native to Argentina (Konno, C., Lu, Z. Xxue, H., Erdelmeier, A., Kersuriyen, D., Che, C., et al.,1990; Gnabre, J., Brady, J., Clanton, D., Ito, Y., Dittmer, J., Bates, R., et al.,1995; Verastegui, M., Sanchez, C., Heredia, N., Garcia-Alvardo, J., 1996; Anesini, et al, 1997). This distinction may be important **if** the two species have different chemical components, thus differing properties.

Creosote bush reproduces both vegetatively and sexually, and some creosote bush clones may be the earth's oldest living organism (Buche, 1997; USDA, Forest Service, 1997). Estimates of the age of the largest clone in Johnson Valley, California, is 9,400 years (Zekes,1999), while others claim bushes carbon-dated to 11,500 years old, were found in the Imperial Valley, California (Buche, 1997; Moore, 1989). McAuliffe estimated the average longevity of creosotebush to be 1,250 years at a study site in Dateland, California, and 625 years at a San Luis site. (McAuliffe, 1994). Creosote bush is an allelopathic shrub, with slow growth cycles and

strategies for surviving with little or no rainfall and even being moderately freeze-resistant.(Botkin, 1949;). The leaves and stems of creosote bush contain a supply of gums and resins, protein, partially characterized esters, acids, alcohol, a small amount of a mixture of sterols, sucrose, and some volatile oils (Botkin, 1949; Mabry, 1977; Buche, 1997). However, the primary chemical in the creosote bush is NDGA (nordihydroguaiaretic acid), a potent antioxidant, anti-inflammatory agent and anticarcinogenic agent.

The biochemical and molecular literature on plants as natural products categorizes organic compounds in plants "that are not directly involved in primary metabolic processes of growth and development" (Croteau, Kutchan & Lewis, chp. 24, pg. 1) as secondary metabolites. Most of these secondary metabolites are defensive mechanisms for the plants. However they are of increasing significance for human health, as we learn of their health-promoting properties. Natural products can be classified into three major categories, i.e., terpenoids, alkaloids, and phenolic compounds. The phenolic compounds are of interest in this research. While phenolic compounds are responsible for the flavor, taste, color, texture and nutritional quality of food, it is other properties that may dramatically affect human health. Phenolic plant compounds have antioxidative and anticarcinogenic activities in experimental animal models, and possibly in humans. (Ho, 1992). Nordihydroguaiaretic acid is a polyphenolic compound with multiple biological activities, 34 of which are listed in the Phytochemical and Ethnobotanical Database of the Agricultural Research Service, United States Department of Agriculture (Duke, 2001) and reproduced in Appendix D.

The long history of NDGA's clinical use continually crosses boundaries between herbal, naturopathic medicine and traditional, allopathic medicine. Likewise, information on the source plant chaparral or creosote bush crosses many boundaries, from Native Indian folklore to the

scientific laboratories of the USDA, the Agricultural Research Services, and the National Institutes of Health. A time-line on the naturopathic history of NDGA begins in pre-recorded history, when methods of healing and care of the sick were transmitted in oral form by indigenous peoples of North America, South America and Mexico (Mabry, 1977). Evidence of early use is recorded in South American, North American and Mexican cultural histories (Anesini & R-Perez, 1993; Beckstrom-Sternberg & Duke, 1992; Stoffle, Halmo, Evans & Olmsted, 1990; Vogel, 1990). Nordihydroguaiaretic acid is derived from the creosote bush, also known as "greasewood', "chaparral", "gobernadora" or "Hediondilla" (McDonald, 1995). Methods for utilizing most of the components of the creosote bush are now found recorded in anthologies of herbal medicine (Heinerman, 1983;Hutchens, 1982), in home-remedy publications (Welburn, 1999: Zekes, 1999), and in electronic communication form via the Internet (Buche, J., 1999; McDonald, 1995; Stansbury, J., 1997). The leaves and stems are considered by native peoples, naturalists and herbalists to be the medicinal parts of the bush, and were frequently boiled and steeped to provide a tea in treatment of a variety of ailments. The modern list of uses include: treatment of acne and skin conditions of warts and blotches, arthritis, cancer, chronic backache, kidney infections, leukemia, prostate gland enlargement, skin cancer, sinusitis, stomach cancer, respiratory problems, plus claims for increasing hair growth, improvement in eye sight, weight reduction (Hutchens, 1982). Scientific work by Botkin and Duisberg (1949) conducted at the Agricultural Experiment Station in New Mexico confirmed the NDGA content in the leaves and green stems (12.3%, 9.6%, respectively) to be the highest in the various parts of the creosote bush. In 1988, Downum, Dole & Rodriguez reported similar results from creosote bush collected in the Sonoran Desert. They also reported seasonal influence on NDGA concentration, with variation possibly due to rainfall, solar irradiation and temperature

(Downum, 1989). The latest study (2002) by Hyder, Fredrickson, Estell, Tellez and Gibbons showed NDGA's highest concentrations in leaves (38.3mg/g) and green stems (32.5mg/g). Phenolics and condensed tannins were present throughout the plants (Hyder, et al., 2002) Indian tribes of the southwestern states boiled the leaves and branches for bruises and rheumatism, and applied dry heated leaves and branches as a poultice to the chest and for other body pain (Hutchens, 1982).

The general and scientific literatures have diverse reports on the clinical effects of NDGA. One case in which ingestion of NDGA extracted from the creosote bush resulted in an unusual cure for malignant melanoma of the cheek is supported by several medical physician's assessments and follow-ups (Smart, 1970). Conversely, severe adverse effects have been attributed to NDGA, with two cases of severe hepatitis and liver failure reported in individuals in Texas and California (Texas Preventable Disease News, Texas Department of Health, 1992; Lawrence Review of Natural Products, 1993; Gordon, 1995; SmartBasics, 1999). Closer examination of these reported cases easily showed they were not sufficiently investigated to eliminate other causes of the liver problems. However, by 1992, the reports were sufficient for the American Herbal Products Association (AHPA) to recommend that members voluntarily suspend sales of the herb chaparral (HealthWorld Online, 1999). This action decreased the sale of chaparral in the U.S., but proponents of healthy living continued to buy supplies in Canada. The use of chaparral has continued, and a truly significant amount of scientific research on NDGA has become available to the public via the Internet. Also, publications of health magazines using natural sources may have re-newed interest in the desert plant, *Larrea tridentata.* Whatever the cause, it can be surmised that dissemination of information on scientific evaluation of the chaparral plant will be forthcoming. In February 1995, the AHPA rescinded its

ban on chaparral and created a hotline for consumers to report potential adverse effects (HealthWorld Online, 1999). The report by Clark Watts, M.D., J.D. stated "...no clinical data were found in the medical records to indicate that chaparral is inherently a hepatic toxin. Moreover, each patient had a medical history not incompatible with prior liver disease..." (HealthWorld Online, 1999, pg.1).

Chemical History of NDGA

Various online databases were searched for information to establish a timeline for (1) the chemical history of NDGA; (2) the food and nutrition-related history of NDGA; and (3) the clinical history of NDGA use**.** A search for the chemical data was initially provided by references in the Merck Index, 12th ed. (Budavari,1996), on the history of major developments in the identification, isolation and synthesis of NDGA. According to Budavari (1996), in 1897 and 1898, Herzig and Schiff described the chemical structure of a substance obtained by ether extraction from guaiacum resin (a closely related species of the Zygophyllaceae family), as guaiaretic acid; later chemists (Schroeter, Lichten, Stadt, & Irineu, 1918) showed the substance to be norhydroguaiaretic acid. These were the first steps in defining the structure of NDGA. In 1934 Haworth and Richardson prepared a synthetic dimethyl ether of guaiaretic acid that, on reduction and demethylation, yielded NDGA. This provided proof of the structure. In 1947 Lieberman, Mueller and Stiller described a new synthesis of NDGA in the laboratory, which confirmed the structure of the prior syntheses. They filed a U.S. patent (Mueller, Stiller & Lieberman, #2,456,443, 1948) to secure their work on NDGA. In subsequent years, several reports of syntheses of NDGA appeared in the literature, i.e., Schrecker, 1957; Blears & Haworth, 1958; Minato, 1980). I. A. Pearl filed patent #2,644,822 in 1953, assigned to Sulphite Products Corporation, which was to improve the process of synthesizing NDGA and related

compounds. In 1962 J. R. Chipault provided the following structural configuration of NDGA (pg. 496):

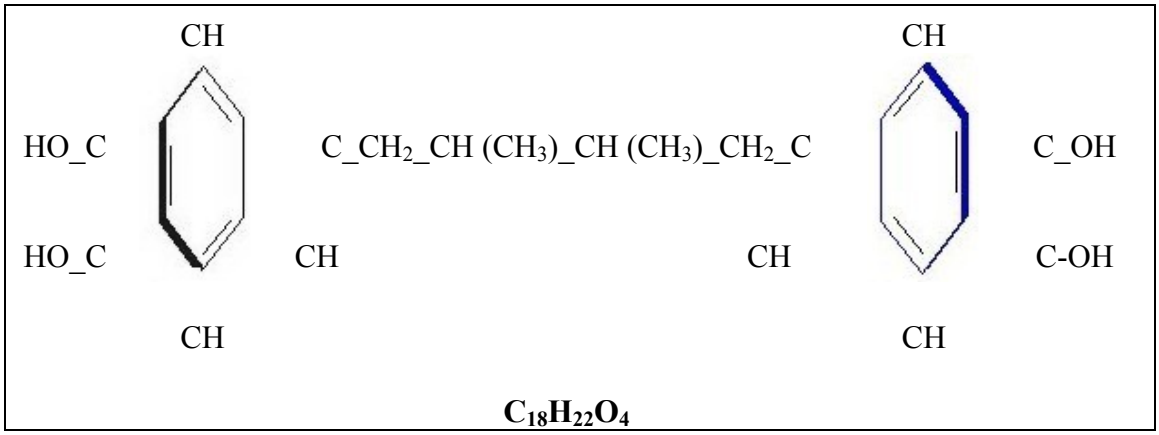


Figure 1: Structural Configuration of NDGA.

Waller and Gisvold made the first recorded isolation claim of NDGA from a natural substance in 1945, when they conducted a phytochemical investigation of *Larrea divaricata* Cav., Family Zygophyllaceae. They identified a crystalline phenol extracted from the powered plant material of the *Larrea divaricata* as nordihydroguaiaretic acid. In the same year, two patents were filed: (1) by W.M. Lauer, assigned to the USDA (#2,373,192, 1945), for use of NDGA as an antioxidant in lard and rendered pork fat; and, (2) (#2,382,475, 1945), by O. Gisvold, assigned to the University of Minnesota, for the extraction process. A comprehensive analysis of the NDGA content of *Larrea divaricata*, as related to geographical location and bush component, was performed by Botkin and Duisberg in 1949, and their information has subsequently been incorporated into most studies of the chemical and its origin in nature.

During this period of time, NDGA was being used as an antioxidant in foods, and the only commercial source was the creosote bush, as synthetic production was too expensive or too complicated to be profitable. Then, in 1972, Perry, Kalnins, and Deitcher developed and patented

a practical synthesis of NDGA "utilizing a novel and highly stereoselective alkylation reaction to form the lignan carbon skeleton." (1972, pg.4371). Working for Hoffman-La Roche Inc., in chemical research, Perry et.al. filed U.S. patent # 3,769,350 (1973) on synthesis of the lignan nordihydroguaiaretic acid.

C.V. Perry, Kalminz & Deltcher are credited with establishing the configuration of the naturally occurring form of NDGA (1972) as the *meso* rather than the *racemic* form, and with synthesis of the lignan structure as previously noted. In the chemical and research literature, various isomers of NDGA are used in projects. The molecular formula and structure for the *meso* and racemic forms are given in Table A.

1. Molecular formula for the naturally occurring *meso* form of NDGA: $C_{18}H_{22}0_4$

   Structure: 1,4-Bis(3,4-dihydroxyphenyl)-2,3-dimethylbutane
   (Schroeter, Lichtenstadt,& Irineu, 1918; Perry, et al., 1972).

2. Molecular formula for the racemic form of NDGA: $C_{22}H_{26}O_6$

   Structure: 2,3-Bis (3,4-dimethoxybenzoyl) butane
   (Perry, et al.,1972).

Table A: Molecular and Structural Formulas for NDGA

Nutrition and Food-Related History of NDGA

Nordihydroguaiaretic acid is used extensively in research projects in the U.S. and abroad, as a prototype antioxidant, and for its many other properties. Both the naturally occurring substance from the creosote bush and laboratory-synthesized supplies are used in food manufacturing and research. Sigma-Aldrich, Fluka Division and Oxford Biomedical Research are chemical suppliers for research projects. The creosote bush is harvested on the public lands in Texas,

Arizona, Utah and New Mexico, as well as being farmed specifically for harvesting. Cultivation of the creosote bush as a soil erosion prevention measure was practiced in the 1950's. Other practical uses of *Larrea tridentata* include its use as a stabilizer of polymers, lubricants, rubber, perfumery oils, and olive husks; as a developer in photography and rust inhibitor. NDGA is also used as a fungicide and as a tumor inhibitor (Oliveto, 1972).

The utilization of NDGA in the most of the food supply in the United States was discontinued in 1968; however American companies continue to use NDGA in lard and animal shortenings and in products exported to other countries. In 2001, twenty other countries continued to allow NDGA in the food supply. These countries are: (1) Austria; (2)Argentina; (3) Bangladesh; (4) Denmark; (5) Finland; (6) Guyana; (7) Haiti; (8) India; (9) Japan; (10) Mexico; (11) Nicaragua; (12) Norway; (13) Pakistan; (14) Panama; (15) Paraguay; (16) Russia; (17) Taiwan; (18) Tobago; (19) Trinidad; and (20) Yugoslavia (Letherhead Food Research Association, 2001; Jadhav, Nimbalkar, Kulkarni, & Madhavi, 1996). It is precisely this discontinued use of NDGA in the food supply in the United States that is the reason for this knowledge synthesis endeavor.

NDGA's use as an antioxidant has been widely researched in the food sciences and in biological research. One of many naturally occurring antioxidants, NDGA is considered a very potent antioxidant and was used extensively in the food supply from 1945 through 1968. The uses of antioxidants as additives to the food supply begin in the 1940's. A substance related to NDGA, gum guaiac, was the first antioxidant approved for the stabilization of animal fats (Madhavi, Deshpande, Salunkhe, 1996). Antioxidants retard the onset of lipid oxidation in food products, thus enhancing the shelf life of many food products, without altering taste or nutritional value.

Autoxidation is the term used to refer to the reaction process of a lipid molecule with a molecule of atmospheric oxygen. Once initiated this chemical process will continue, forming free radicals in what is known as a *free-radical chain reaction*. "Free radicals have been defined as a molecular entity possessing an unpaired electron." (Jadhav, Nimbalkar, Kulkarni, & Madhavi, 1996, pg. 9). The chemical symbol for the organic free radical is: R·. Autoxidation is the process by which atmospheric oxygen reacts spontaneously with a number of organic compounds and causes structural degradation, resulting ultimately in loss of quality of numerous chemical products of economic or industrial importance. In the food supply, spontaneous oxidative reactions result in deterioration of lipids. Autoxidation of lipids in the food chain and in biological systems occurs in a similar manner. The process of oxidation and free radical formation in foods will be discussed here. Free radical formation in biological systems will be discussed later. Autooxidation is a natural phenomenon in the food supply, and is retarded to a certain extent by the naturally occurring antioxidants. However the processing and storage of foods causes the loss of natural antioxidants, requiring the addition of exogenous antioxidants. Dietary lipid oxidation in foods is catalyzed by heat, light, ionizing radiation, trace metals (especially copper and iron), metalloproteins (i.e., heme), and also enzymatically by lipoxygenase. There are three distinct stages in the process of autoxidation: initiation, propagation, and termination. Initiation of the autoxidation of a fat begins with the formation of an organic free radical [symbol = R·]. When in contact with oxygen, an unsaturated lipid forms organic free radicals as depicted in equation I: * (see LEGEND* for symbol interpretation)

LEGEND: *	
O^2	Superoxide
H	Hydrogen
HO_2	superoxide

	conjugate acid
IO^2	singlet oxygen
OH	hydroxyl radical
R·	organic free radical
ROO·	peroxy free radical

Equation I: O_2 + H (extracted from fatty acid) or RH (substrate) → R• + H•

The next occurrence (Equation II and III *) may be the break down of lipid hydroperoxide, which exists in trace quantities prior to the oxidation reaction:

Equation II: ROOH ——> RO· + HO·

Equation III: 2ROOH → RO· + ROO· + H_2O

The hydroperoxides undergo bimolecular decomposition. Lipid hydroperoxides are formed by various pathways including the reaction of singlet oxygen [IO_2] with unsaturated lipids or the lipoxygenase-catalyzed oxidation of polyunsaturated fatty acids (Jadhav, et al, 1996; Awasthi, Singhal,& Awasthi, 1996).

In propagation, the second stage, organic free radicals are converted into other radicals, in a chain reaction. The chain reaction is a general feature of the reactions of free radicals. The propagation of free-radical oxidation processes in lipids is a chain reaction of oxygen consumption and formation of new free-radical species, i.e., peroxyl radicals [ROO·] or the formation of peroxides [ROOH], as in Equation IV and V*:

Equation IV: R· + $^3O_2$ —> ROO·

Equation V: ROO· + RH —> ROOH + R·

The products R· and ROO· can further propagate organic free-radial reactions (Jadhav et al, 1996). Reactions with other fatty acids and free radicals also occur, with these equations depicting only one possible process.

The third stage of autoxidation is termination, or the bonding of the unstable free radical, which will stop the process. Free radicals are highly reactive and tend to react whenever possible to restore normal bonding. In the absence of unsaturated lipids (or fatty acids), radicals bond one to another, forming a stable, nonradical compound. The following three equations (from Ardestani, Ahadian & Watson, 1996, pg. 185) depict this termination reaction:

Equation VI: R· + R· —> R—R
Equation VII: R· + ROO· —> ROOR
Equation VIII: ROO· + ROO· —> ROOR + O_2

This termination reaction leads to interruption of the chain reaction.

The process of autoxidation of lipids in foods can be prevented and/or delayed by the use of antioxidants, usually in small amounts. Lipids are one of the major constituents in foods and other biological systems. Lipids are organic biomolecules, classified into three major groups, with sub-groupings. These groupings become important in understanding the role of antioxidants in biological systems, as well as in food science. Table B below organizes lipids into groups and subgroups, with a listing of some of their functions.

LIPID GROUP	SUBGROUP	BIOLOGICAL FUNCTION
Simple lipids	triglycerides	energy storage
	steryl esters	
	wax esters	
Compound lipids	Phospholipids	membrane structure
	Glycolipids	membrane structure
	Sphingolipids	membrane structure
	Lipoproteins	
Derived lipids	fatty acids	
	fat-soluble vitamins	
	Provitamins	
	Sterols	membrane structure
	Terpenoids	
	Ethers	

Data from Jadhav, et al. (1996). Lipid oxidation in biological and food systems. In D. Madhavi, S. Deshpande & D. Salunke (Eds), *Food Antioxidants, Technology, Toxicological and Health Perspectives.*

Table B: Lipids and their Function in Biological Systems

Lipids are found in many foods of plant origin, and these are highly unsaturated lipids. Lipids in animal sources have lower levels of unsaturated lipids, but contain certain amounts of higher unsaturated fatty acids. It is the unsaturated fatty acids, which make lipids susceptible to oxygen attack and autoxidation. Thus animal fats are highly susceptible to early and extensive autoxidation. Substances that retard oxidation are known as antioxidants; substances that shorten the induction period for deterioration are known as proxidants. "The use of antioxidants in lipid-containing foods minimizes rancidity, retards the formation of toxic oxidation products, and allows maintenance of nutritional quality and an increase in shelf life of a variety of lipid-containing foods." (Jadhav, et al., 1996, pg.6).

The use of antioxidants in the food supply chain began in 1940 with the addition of guaiac gum. Since then numerous natural antioxidants have been identified and tested for use in the food supply chain. Most natural antioxidants are phenolic compounds, and NDGA is in this

category. NDGA has a history of use as a food preservative, antioxidant and additive. Reference to these properties has been made by the USDA, food science publications (Madhavi, et al., 1996; Watson & Mufti, 1996; Hudson, 1990), and the Hormel Institute (Lundberg, 1962). Lundberg, Halvorson and Burr first described the antioxidant properties of NDGA in 1944. It is a typical phenolic antioxidant, more active in animal fats than vegetable oils. In 1945, W.M. Lauer patented NDGA for the Meat Inspection Branch of the USDA, for use in lard and rendered pork fat (U.S. Patent #2,373,192). NDGA was used in the food supply from 1945 to 1968, as a preservative for fats, oils, and meat, (Madhavi, et al., 1996)), to prevent rancidity and extend the shelf life. The USDA and the United States Army also conducted studies on autoxidation and the use of antioxidants. (Lundberg, 1962; Andrews, 1965).

While there were a number of early researchers working in the field of autoxidation and antioxidants, Dr. W. O. Lundberg probably contributed the most to the primary research, the compilation of the research, and the scholarly recording of the research results (Lundberg, 1962, vol.2). He was the first to describe the antioxidant properties of NDGA (Lundberg, Halvorson & Burr, 1944), and continued to work on describing the other properties of NDGA. The following is a compilation of Lundberg's work, which describes the physical properties of NDGA:

Properties of Nordihydroguaiaretic acid

Formula: $C_{18}H_{22}0_4$

Molecular weight: 302.36

D*escription:* Tan powder (when extracted from creosote bush); greyish-white crystalline substance when pure and/or synthesized.

Solubility: Slightly soluble in hot water and dilute acids. Soluble in dilute alkali, fats 0.5-0.7% @ (20^0C), and fats & oils 5% when heated to 125 - 150^0C. Soluble in ethanol, propylene glycol

Melting point: 184 - 185 ^{0}C

Source: Chipault, pg.496-7, in Lundberg, Volume II, (1962).

Four hundred forty-seven U.S. patents on nordihydroguaiaretic acid are listed in the United States Patent and Trademarks Database, dated from 1945 to 2001. In some patents NDGA is an additive rather than the primary substance of the patent. In addition to its use as an additive in food products, NDGA is used as a stabilizer in pharmaceutical preparations, perfumery oils, rubber and other industrial products (Oliveto, 1972).

Clinical History of NDGA Use

The clinical history of NDGA is extensive, complex and on going. The medicinal properties of the creosote bush have been recognized for hundreds of years. Herbal remedies for an extensive list of aliments have been practiced by the Native Americans, Indians in Mexico, cross-cultural groups in the Southwestern United States and by an increasing consumer base of middle-class Americans. The empirical use of NDGA as an anti-infective, anti-inflammatory, anti-carcinogenic agent has largely been supported by scientific research that describes the anti-viral, antibiotic, and antioxidant properties of NDGA. Herbal enthusiasts and consumers have complied a list of fourteen (14 +/-) conditions in which preparations from the creosote bush have cured or ameliorated the symptoms (Moore,1989; Snyder,1996; Buche, 1999; Stansbury, 1997 & 1999; Stoffle, Halmo, Evans, & Olmsted, 1990). While some have began to criticize and express disdain at the multiple treatments provided by creosote bush and NDGA, a critical analysis of the scientific communities literature should abate this trend. Therefore Table C is presented below to show the links between the patient problems as documented in the popular literature, the scientific explanation of NDGA's properties, and reference(s) for verification and further reading.

PATIENT PROBLEMS	SCIENTIFIC PROPERTIES	RESEARCH REFERENCES
1. Infections • various skin infections • kidney infections • colds/flu • warts	1.Antiviral and antibiotic	1.1 Hwu, J.,et al (1998). Antiviral activities of methylated nordihydroguaiaretic acids. Synthesis, structure identification and inhibitation of tat-regulated HIV transaction. 1.2 Segura, J.(1998). Effects of nordihydroguaiaretic acid and ethanol on the growth of Entamoeba invadens. 1.3 Verastegui, M. (1996). Antimicrobial activity of extracts of three major plants from the Chihuahuan desert (Agave lecheguilla, Baccharis glutinosa, & Larrea tridentata).
2. Autoimmune conditions • arthritis • rheumatism acne	2. Inhibits 5-HETE,which is present in synovial fluid in arthritics	2.1 Fischer, S. (1997). Prostaglandins and cancer.
3. Gastrointest-inal imbalances • diarrhea • stomach pain • nausea vomiting • steratorrhea • intestinal • parasites	3. Stabilizes gastrointest-inal tract	3.1 Agarwal, R., Wang Z., Bik. D., Mukhtar, H (1991). Nordhydroguaiaretic acid, an inhibitor of lipogenase, also inhibits cytochroje P-450-mediated monooxygenase activity in rat epidermal and hepatic microsomes. 3.2 Segura, J (1978). Effects of nordihydroguaiaretic acid and ethanol on the growth of Entamoeba invadens.
4.Respiratory problems • allergies • bronchitis • asthma • sinusitis	4. Stablizes mast cells	4.1 Maloff, B., Fefer, D. Cooke, G. & Ackerman, N. (1987). Inhibition of LTB4 binding to human neutrophils by nordihydroguaiaretic acid. 4.2 Salvaggio, J. (1990). Recent advances in pathogenesis of allergic alveolitis.

PATIENT PROBLEMS	SCIENTIFIC PROPERTIES	RESEARCH REFERENCES
5. Pain	5. Analgesic	5. Sneed, P. (1999). Personal Communication.
6.Anti-aging • grow more hair • weight loss	6. Inhibition of accumulation of lipofuscin	6.1 Munkres, K. & Rana, R. (1978 a & b). Ageing of neurospora crssa. VII. Accumulation of fluorescent pigment (lipofuscin) and inhibition of the accumulation by nordihydroguaiaretic acid. 6.2 Nagano, N., et al. (1996). Opening of Ca2+-dependent K+ channels by nordihydroguaiaretic acid in porcine coronary arterial smooth muscle cells.
7. Neoplastic growths • cancer • leukemia • enlarged prostrate • skin cancer and actinic keratoses	7. Antimutagenic and anti-tumorigenic	7.1 Ansar, S., et al. (1999). Nordihydroguaiaretic acid is a potent inhibitor of ferric-nitrolotriacetate-mediated hepatic and renal toxicity, and renal tumour promotion, in mice 7.2 Arias-Diaz, J., et al. (1994) Tumor necrosis factor-alpha-induced inhibition of phosphatidylcholine synthesis by human type II pneumonocytes is partially mediated by prostaglandins. 7.3 Baba, T., et al. (1992). The effect of 5-lipooxygenase inhibition on blood-brain barrier permeability in experimental brain tumors. 7.4 Barnby, J., Styles, A., Cockerell, C. (1997) Actinic keratosis: Differential diagnois and treatment. 7.5 Birkenfeld, S., et al. (1986). Antitumor effects of inhibitors of arachidionic acid cascade on experimentally induced intestinal tumors. 7.6 Denizot, Y., et al. (1993). Effect of eicosanoids metabolism inhibitors on growth of a human gastric tumour cell line (HGT). 7.7 Earashi, M., et al. (1996). In vitro effects of eicosanoid synthesis inhibitors in the presence of linoleic acid on MDA-MB-231 human breast cancer cells. 7.8 Emerit, I., et al. (1983). Suppression of tumor promoting phorbolmyristate acetate-induced chromosome breakage by antioxidants and inhibitors of arachidonic acid metabolism.

PATIENT PROBLEMS	SCIENTIFIC PROPERTIES	RESEARCH REFERENCES
(continue with #7	(continue with antitumorigenic and antimuta-genic properties)	7.9 Frasier, L. & Kehrer, J. (1993). Effect of indomethacin, aspirin, nordihydroguaiaretic acid and piperonyl butoxide on cyclopposphamide-induced bladder damage. 7.10 Gati, I., et al. (1990). Effects of prostaglandin and leukiotriene inhibitors on the growth of human glioma spheroids. 7.11 Johanning, G., Lin, T. (1995). Unsaturated fatty acid effects on human breast cancer cell adhesion. 7.12 Kunkel, S., et al. (1984). Role of lipoxygenase products in murine pulmonary granuloma formation. 7.13 Madrigal-Bujaidar, et al. (1998). In vivo and in vitro antigenotoxic effect of nordihydroguaiaretic acid against SCE's induced by methyl methanesulfonate. 7.14 McCormick, D., et al. (1987). Nordihydroguaiaretic acid suppression of rat mammary carcinogenesis induced by N-methyl-N-nitrosourea. 7.15 Moody, T., et al. (1998). Lipooxygenase inhibitors prevent lung carcinogenesis and inhibit non-small cell lung cancer growth. 7.16 Nakadate, T., et.al. (1982). Inhibition of 12-0-Tetradecarnoylophorbol-13-acetate-induced epidermal ornithine decarboxylase activity by physopholipase A2 inhibitors and lipoxygenase inhibitors. 7.17 Noguchi, M.,et al.(1995). The role of fatty acids and eicosanoid synthesis inhibitors in breast carcinoma. 7.18 Onoda, J., et al. (1994) Inhibition of radiation-enhanced expression of integrin and metastatic potential in B16 melanoma cells by a lipoxygenase inhibitor. 7.19 Palmantier, R., et al. (1996). Regulation of adhesion of a human breast carcinoma cell line to type IV collagen and vitronectin: Role of lipoxygenase and protein kinase C.

PATIENT PROBLEMS	SCIENTIFIC PROPERTIES	RESEARCH REFERENCES
		7.20 Parry, E. (1993). Cycloheximide or nordihydroguaiaretic acid protects mice against the lethal and hepatocytolytic effects of a combined challenge with D-galactosamine and bacterial endotoxin. 7.21 Pavini, M., et.al. (1994). Inhibition of tumoral cell respiration and growth by nordihydroguaiaretic acid. 7.22 Reddy, N., et al. (1997). Characterizatio of a 15-lipoxygenase in human breast carcinoma BT-20 cells: Stimulation of 13-HODE formation by TGFa/EGF. 7.23 Rillema, J. et.al. (1997). Effect of NDGA, a lipoxygenase inhibitor, on prolactin actions of mouse mammary gland explants. 7.24 Wilson, D., et.al. (1989). Effect of nordihydroguaiaretic acid on cultured rat and human glioma cell proliferation.

Table C: Correlation of Patient Problems with NDGA Research.

Scientific Properties of NDGA

In biological systems, NDGA has multiple affects and functions, the earliest and best known of which are the antioxidant properties that enable it to function as a lipoxygenase inhibitor. Understanding the properties of NDGA requires some selected background information on the physiology of the human, and the biochemical pathways that are affected or changed by NDGA. The biochemical pathways are summarized in Table D.

Biochemical Properties of NDGA
• 5-lipoxygenase inhibitor • inhibits arachidonic acid • inhibits metabolism and synthesize of eicosanoids • 5-HETE (5-hydroxyeicosatetraenoic acid) inhibitor • preferential inhibitor of PDGF (platelet derived growth factor) • depletes intracellular ATP in liver studies • inhibitor of biosynthesis of thromboxane A_2

Note. From: McCormick & Spicer, 1987;Bhattacherjeee, Boughton-Smith, Follenfate, Garland, Higgs, Hodson & Jackson, 1988; Wilson, DiGianfilippo, Ondrey, Anderson, & Harris, 1989; Wang, Agarwal, Shou, Bickers & Mukhtal, 1991; Nakayama, Hori, Osawa

& Kawasishi, 1992; Domin, Higgins, & Rozengurt, 1994; Avis, Jett, Boyle, Vos, Moody, Teston, Martinez, & Mulshine, 1996; Moody, Leyton, Martinez, & Hong, 1998; Diaz, Madrigal-Bujaidar, & Marquez, 1999; Lambert, Ross, Timmerman, & Dorr, 2001; Seufferlein, Schwarz, Beil, Wichert, Baust, Luers, Schmid & Adler, 2002.

Table D: Summary of Biochemical Properties of NDGA

All of these biochemical properties translate into the following clinical effects: NDGA is (1) an antioxidant and free radical scavenger, (2) an anti-inflammatory agent, (3) antimutagenic and (4) antitumorigenic. The clinical effects of NDGA have been tested *in vivo* on laboratory research animals (i.e., mice, rats, guinea pigs) with experimentally induced carcinogenic tumors (e.g., Moody, Leyton, Hong, Malkinson & Mulshine, 1998; Pavani, Fones, Oksenberg, Garcis, Hernandes, Cordano, et al., 1994; Rao, Baas, Glasgow, Eling, Runge & Alexander, 1994; Baba, Chil & Black, 1992; Gati, Bergstrom, Westerber, Csoka, Muhr & Carlsson, 1990; McCormick & Spicer, 1987; Rillema, 1984; Nakadate, Yamamoto, Ishii & Kato, 1982). Numbers of *in vitro* research studies have been conducted on cultured human breast cancer cells (e.g., Palamtier, Roberts, Glasgow, Eling & Olden, 1996; Reddy, Everhart, Eling & Glasgow, 1997: Earashi, Noguchi & Tanaka, 1996; Earashi, Noguchi, Kinoshita & Tanaka, 1995;Johanning & Lin, 1995;Noguchi, Rose, Earashi & Miyazake, 1995). The selected studies cited here and in Table D provide only a beginning profile of the research data on NDGA. The beneficial effects of NDGA, as well as the toxic effects are well documented; however, dissemination of this information and incorporation into the clinical treatment literature is virtually absent. Likewise, refutation and clarification of the earlier studies reporting toxic effects of NDGA have not been forthcoming. A brief explanation of the biochemical effects of NDGA as supported by biomedical and chemical research will be presented.

In a generalist sense, the biochemical pathways of the body are primarily of a cascade-formation, either a mandatory pathway, or a modified-cascade process with alternative pathways

to initiate some intermediate processes. The normal state of biological equilibrium moves from maintenance to defense when disruption occurs. The major bodily mechanism of self-defense or response to disruption is the inflammatory response. The inflammatory response is a complex, non-specific biochemical and cellular process that occurs in vascularized tissues. The inflammatory response occurs in the same way regardless of the stimulus, and is not memory based. Cellular injury stimulates the inflammatory response, i.e., trauma from mechanical forces, oxygen or nutrient deprivation, genetic or immune defects, chemical agents, microorganisms, temperature extremes, or ionizing radiation. Inflammation will also occur in response to the presence of dead cells--the host cells, microorganisms, or cells of dead parasites. Specialized cells and protein systems in the plasma are the key players in the inflammatory response. In concert with cells and platelets at the site of injury, three major plasma protein systems (the complement, clotting, and kinin systems) and immunoglobulins, are involved in the inflammatory response. Specialized cells, the mast cells, located in the loose connective tissues close to the blood vessels, are cellular bags of granules containing vasoactive amines and chemotactic factors. While the list of vasoactive amines and chemotactic factors is extensive, the focus here will be on substances affected by NDGA, and they will be depicted in graphs and charts as a means of clarification to explain the interaction.

One of the steps in the inflammatory response is lipid oxidation. In cellular systems, lipid oxidation can occur in the biomembranes of the cell, i.e., membranes surrounding the cell, and membranes surrounding occlusions in the cell, e.g., microsomes and mitochondria. The process is known as lipid peroxidation. It is similar to autoxidation in dietary substances, but involves more factors, some of which have not been elucidated. Factors which induce the prooxidant state, i.e., support autoxidation, include: (1) hyperbaric oxygen tension; (2) ionizing radiation;

(3) xenobiotic metabolism and certain chemicals; (4) stimulation of hydrogen peroxide-generating oxidases (peroxisome proliferators); (5) membrane active agents; and (6) inhibition of the antioxidant defense systems (Jadhav, et al, 1996). Lipid peroxidation in biomembranes releases reactive oxygen species such as superoxide anions, hydroxyl radicals, hydrogen peroxide, and singlet oxygen. When produced in amounts which overcome the cellular antioxidant defense mechanisms, the biomembranes are destroyed and the function of cellular organelles are loss. The chain-reaction process of peroxidation leads to changes in the DNA, cellular damage and eventually cellular death. A number of diseases are linked to lipid peroxidation. The aging process, cancer, degenerative diseases such as arthritis and atherosclerosis, and general tissue ischemia are considered lipid peroxidation-induced diseases and effects (Bermond, 1990).

Oxidative radials (free radicals) are associated with the inflammatory response seen in many conditions. Lipid peroxides, such as prostaglandins and leukotrienes, are players in the 'arachidonic acid cascade' of the inflammatory response. Arachidonic acid is a fatty acid present in cell membrane phospholipids and triglycerides of all mammalian tissues. Its postulated functions are sustainment of membrane fluidity and as substrate storage. Arachidonic acid is the precursor of prostaglandins and leukotrienes, via the cyclooxygenase and lipoxygenase pathways respectively. (Prostaglandins, hydroxy-fatty acids and leukotrienes are collectively known as *eicosanoids*.) The metabolic pathways for arachidonic acid or the 'arachidonate cascade' are of interest here due to the study of eicosanoids involvement in tumor development, cell proliferation, metastases, and immune surveillance (Fisher, 1997). Leukotrienes and prostaglandins are mediators of inflammation, and are synthesized in the mast cell of vascularized tissues. Leukotrienes are acidic, sulfur-containing lipids that cause smooth muscle

contraction, increase vascular permeability, and attract neutrophils and eosinophils (white blood cells). Prostaglandins also increase vascular permeability and attract neutrophils, plus they induce pain. Prostaglandins are long chain, unsaturated fatty acids produced from arachidonic acid by the action of cyclooxygenase. (Price, 1994). In addition, arachidonic acid metabolites include prostacyclins, thromboxanes, the leukotrienes and hydroxyeicosatetraenoic acid derivatives (HETES), as well as prostaglandins (Wilson, et al., 1989). Arachidonic acid is derived from the phospholipid of many cell membranes when phospholipases are activated by injury or by other mediators (Price, 1994). **Figure 2** graphs arachidonic acid metabolism with intermediate steps included, and identifies inflammatory mediators:

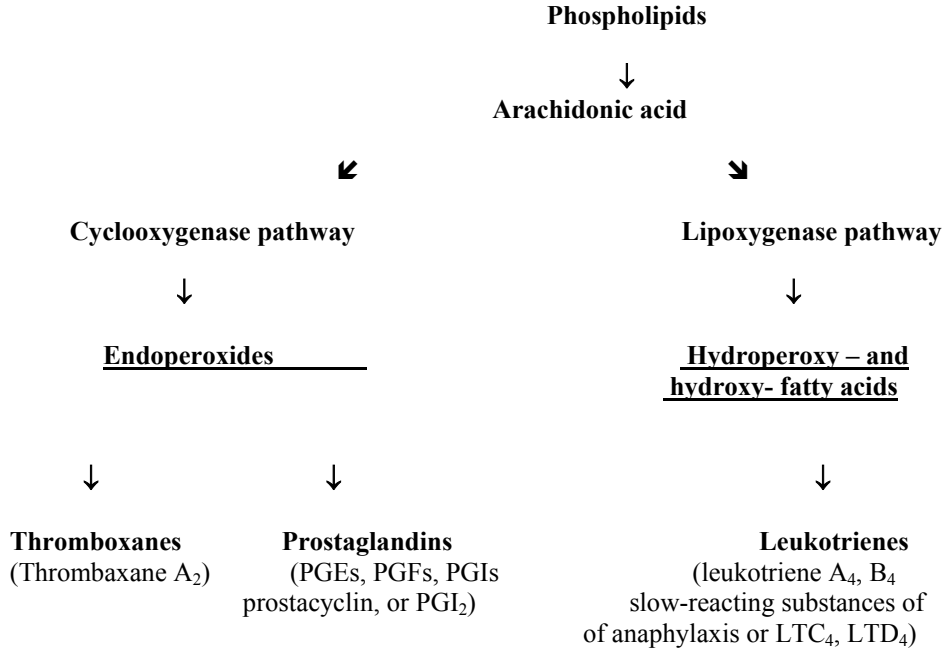
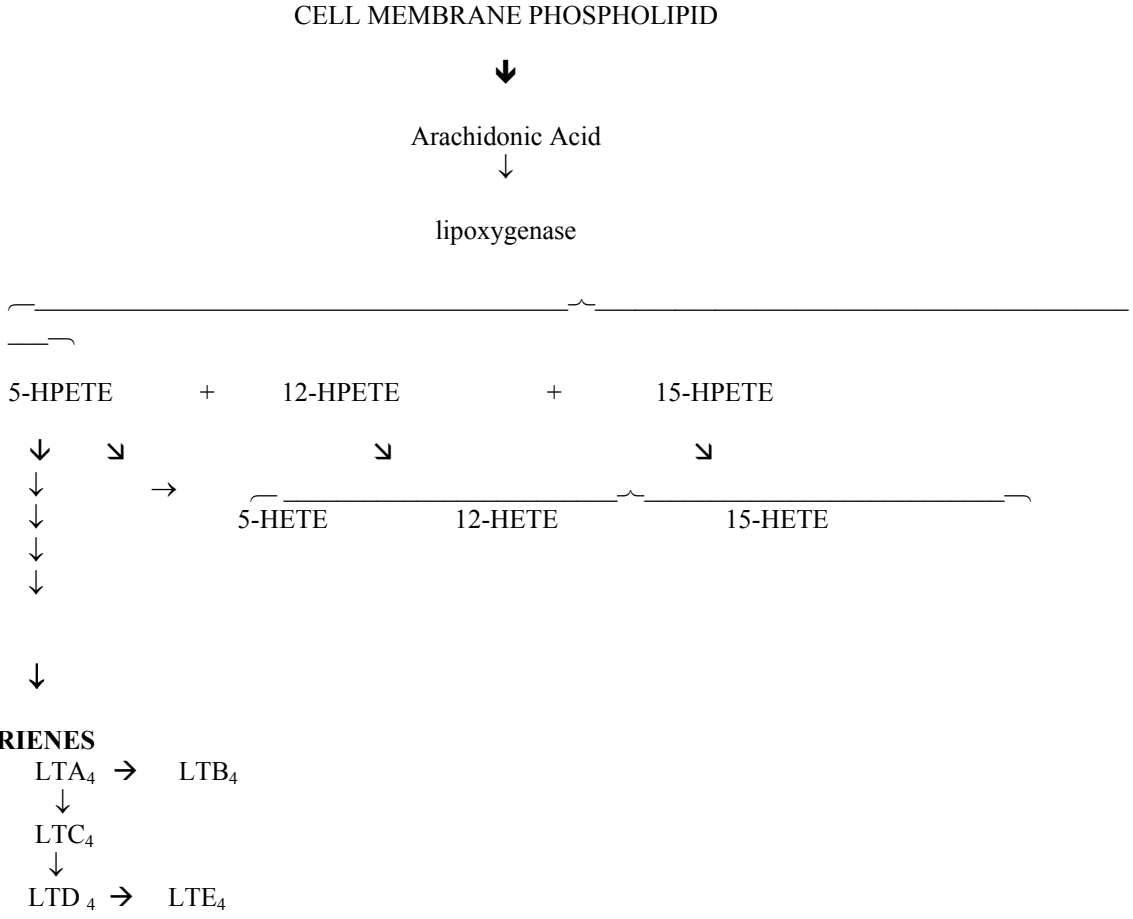
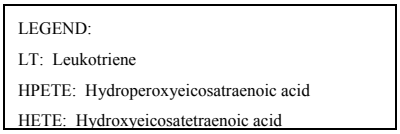


Figure 2. THE ARACHIDONATE CASCADE: Arachidonic acid metabolism and inflammatory mediators. (From: Fischer, 1997, and Price, 1994)

Eicosanoids are involved in a number of pathophysiological conditions in addition to carcinogenesis. Therefore an understanding of the mechanisms by which they are activated is

seminal to research on NDGA. The next graph in **Figure 3** is presented to further elucidate the position of arachidonic acid in the lipoxygenase pathway, as the hydroperoxyeicosatetraenoic acids (HPETE) and hydroxyeicosatetraenoic acids (HETE) and leukotrienes are implicated in diseases such as arthritis, psoriasis, asthma, and leukemia. "Evidence is accumulating that implicates lipoxygenase products as positive or negative regulators of deoxyribonucleic acid (DNA) synthesis in normal lymphocyte mitogenesis..., psoriasis..., neuroblastoma cells..., erythopoietin-stimulated erythroid progenitor cells..., and prostate PC-3 cells... (Wilson, 1989, pg. 551). And NDGA is one of the most potent lipoxygenase inhibitors known. NDGA inhibits eicosanoid metabolism, functioning as an antiproliferative agent, and markedly inhibited the *in vitro* proliferation of glioma cells (i.e., brain cells) in human tissues (Wilson, 1989, p.559). Figure 3 diagrams the lipoxygenase pathway of arachidonic acid metabolism.





Note. From Wilson, D., et al. (1989). Effect of nordihydroguaiaretic acid on cultured rat and human glioma cell proliferation. *Journal of Neurosurgery, 71*, 552.

Figure 3: Lipoxygenase Pathway of Arachidonic acid Metabolism.

Breast Cancer, Functional Foods, and Nutrition

The possible prevention of breast cancer in women by functional foods, e.g., phytochemicals or synthetic additives, is the reason for this study. The literature on human breast cancer commonly begins with pronouncements about the continuing increase in morbidity and mortality in developed countries, followed by notations about the small decreases in mortality seen in the United States related to early detection. As a worldwide public health problem, the incidence of breast cancer in women continues to rise. This has been the pattern since 1935, with significant changes noted among certain populations. “Large variations in the rates of breast cancer among countries and over time within countries and large increases in the rates of breast cancer among populations migrating from nations with a low incidence to those with a high incidence indicate the existence of major nongenetic determinants of breast cancer and the potential for prevention.” (Ardestani, Ahadian, & Watson,1996, pg.173). While the list of risk factors (or those conditions which may increase the potential for development of breast cancer) for breast cancer is long, and the range of factors broad, a consistently present carcinogenic factor has not been specifically elucidated. However, careful analysis of the statement by Ardestani, Ahadian & Watson highlights several factors, which are supported by statistical counts and epidemiological

studies. These factors are: (1) variation of breast cancer rates between countries; (2) large variations of breast cancer rates within countries; and (3) the increase in breast cancer rates among those migrating from nations with a low incidence to those countries/nations with a high incidence.

These factors highlight causative agents or conditions, which are specific to a region and a population. They indicate the presence of substances that are either ingested or present in the environment thereby creating an exposure hazard. Substances ingested, i.e, food and nutrients and additives, are the topic of this research. An enormous body of experimental evidence, metabolic evidence, and epidemiological evidence supports the causative role of food and nutrition in the initiation, promotion, and progression of several types of human cancer, including breast cancer. (Hakim, Leonard-Green & Ritenbaugh, 1996; Greenwald, 1996; ASCN/AIN, 1996; El-Bayoumy, Chung, Richie, Reddy, Cohen, Weisburger & Wynder, 1997; Clavel-Chapelon, Niravong & Joseph, 1997; Trichopoulou & Lagiou, 1997; Dwyer, 1997; Favero, Parpinel & Franceschi, 1998; Synderwine, 1998; Hin-Peng, 1998; DeMarini, 1998; American Dietetic Association, 1999). The strength of dietary factors association with human cancer ranges from 25%, excluding skin cancer (Weisburger & Williams, 1995) to 40% (Wynder & Gori, 1977) in the United States. The American Cancer Society provides evidence to "...suggest that about one-third of the 500,000 cancer deaths that occur in the United States each year is due to dietary factors." (American Cancer Society, 1999a, paragraph 2). And this information is not new. Literature from the early 1900's analytically relates nutrition to possible cancer risk (Williams, 1908).

The process of carcinogenesis is intricately complex. Many environmental substances have been indicated as possible human carcinogens. In fact, "the majority of all human cancers are

considered to be environmentally induced, based on lifestyle patterns, including diet." (VERIS, 1999, p. 2). Chemicals are one group of potential environmental carcinogens that are widely consumed in the human diet. Thus, logic dictates a search for a preventative from the same source.

There is general agreement that one, or more, of four factors are necessary for cancer to develop in individuals. These factors are:

1. Inheritance of defective gene(s).
2. Exposure to carcinogen(s).
3. No substance present to combat a carcinogen.
4. Lack of treatment.

These factors are neither simple nor easily defined. Cancer development is considered to proceed through the stages of initiation, promotion and progression. Thus, an anti-carcinogen and cancer chemopreventative, would interact at specific points in the process of cancer development. Any factor which "retards or interferes with the 'production of carcinogens, their initiation of the cancer process, or the promotion, progression, or metastasis of malignant cells would be considered anticarcinogenic." ((Bailey & Williams, 1993, p. 11). Human epidemiological data is available from multiple sources and studies to confirm the association of reduced risk of some cancers with frequent consumption of certain foods, i.e., functional foods (Doll & Petro, 1981; Greenwald, 1996; Johnson, 1997; Kohlmeier & Mendex, 1997; Hasler, 1998; American Dietetic Association [ADA], 1995 & 1999;Barrett, 2001; Davidson, 2001).

The interrelatedness of the four factors necessary for cancer development is particularly germane to this research. When one looks at the many steps in food production and marketing, and incorporate these into 'dietary factors', i.e., the food, where the food was grown, pesticides

used in cultivation, fertilizers, marketing process, packaging, preservatives, additives, cooking, then factors two (2) and three (3) become primary in prevention of cancer development. The potential for antioxidants in food to function as the 'combant' of carcinogens has been at the center of cancer research for the last 30 years. (Wattenberg, 1992).

Human cancer prevention and protection from development, is inexplicably connected to food and specifically "functional foods'. In the early literature on functional foods and their components, they were defined as food-borne substances that have demonstrated anticarcinogenic effects in experimental systems (Williams & Wynder, 1996). An alternate definition is broader, i.e., foods with physiologically active components, both from plant (phytochemicals) and animal (zoochemicals) sources, including natural and modified food ingredients, that may provide a health benefit beyond the traditional nutrients it contains (ADA, 1999: Milner, 2000). The term "functional foods" as used in this research will be broadly interpreted and inclusive of several related terms which are used interchangeably in the food science, agriculture, nutrition and business, and alternative and complementary therapies literature. Several reasons exist for this inclusion. One, there is not a legal definition of functional foods in the United States. Japan is the only country that has formulated a specific regulatory process for functional foods. Japan introduced the term functional foods in the mid-1980's in reference to processed foods containing ingredients that aid specific bodily functions in addition to being nutritious (Hasler, 1998). A second reason is even without a legal definition, many organizations produce, refine and market functional foods and functional food products, although some are not specifically labeled functional foods. Currently, the term functional foods refer to processed foods containing ingredients that promote certain specific functions within the body (Vasconcellos, 1998). Evolution of the terminology begin in 1989 when Dr. Pierson,

Director of the Program For Designer Foods of The National Cancer Institute coined the term 'designer foods' to describe "foods which contain chemical compounds, either naturally present or added, which are biologically active but non-nutritional, derived from plant sources (phytochemicals), effective in the reduction of the risk of cancer." (Vanconcellos, 1998, pg.3). Later that year, the term 'nutraceutical' was coined by Dr. DeFelice, Director of the Foundation for Innovative Medicine, to refer to "any substance which may be considered a food or part of a food which offers medical health benefits, including the treatment and prevention of a disease" (Vasconcellos, 1998, pg.3). A third reason to include a broad definition of the term functional foods is to limit inadvertent loss of applicable information. The multiple terms used for the one category of food substances, need to be searched in order to perform a comprehensive retrieval and examination of the literatures. Other terms found in the literature which characterize functional foods include: pharmafoods; phytonutrients; medical/medicinal foods; genetically engineered foods; prebiotics; probiotics; genetic foods and therapeutic foods. Another group of substances closely associated with functional foods are the nutritional/dietary supplements, with a sharing of some terms, such as 'nutraceuticals'. Nutritional/dietary supplements are defined by the U.S. Dietary Supplement Health and Education Act (DSHEA) of 1994, and further explained by the National Institutes of Health Office of Alternative Medicine (Minkwitz, 1999). Some distinguishing characteristics of functional foods include the following:

1. In general, functional foods are health promoting and intended to reduce the risk of disease and increase the healthy life expectancy, rather than preventing a deficiency such as with fortified foods.
2. Functional foods may be formed by adding active substances to natural foods after harvesting, or via bioengineering of seeds, or by altering plant growth via agricultural

interventions, i.e., changing soil composition, spraying with chemicals to change growth patterns or stimulate production of protective lignans.

3. Functional foods are consumed as part of a regular, nutritious diet and lifestyle.

Specific functional food components and their source that have been associated with lower rates of breast cancer in humans (Watson & Mufti, 1996) are listed in the Table E, and also in Appendix A.

FOOD COMPONENTS	FOOD SOURCE
1. fiber	1. cereal, bread
2. conjugated linoleic acid	2. cheese, meats
3. indole-carbinol and thiocynatea	3. cruiferous vegetables
4. selenium & flavones	4. vegetables
5. D-limonene	5. citrus fruits
6. Isoflavones	6. soy products
7. soy protein isolate	7. soy

Table E: Functional Food Components Protective for Breast Cancer & the Food Source

In the scientific inquiries related to dietary nutrients and phytochemicals in food, both natural and synthetic antioxidants are considered to have a significant role in breast cancer prevention. (Duke, 1990; Ardestani, Ahadian & Watson, 1996; Hegenbart, 1998; Kreuger, 1998). The destruction of natural antioxidants in food caused by the methods of storage and preparation has lead to the common practice of adding both natural and synthetic antioxidants to food in various stages of processing for the market (Madhavi, Singhai, & Kulkarni, 1996; Despande, Despande & Salunkhe, 1996; Lundberg, 1962). The 'original' source of the functional food component that is an anticarcinogenic agent may be plant, animal, or replacement of lost original source with a synthetic.

Animal studies have shown more than 500 food-derived and synthetic factors that do indeed, inhibit carcinogen response in one or more protocols (Wattenberg, 1990). Watten berg (1990)

and others have classified the chemical agents that block or prevent carcinogen-DNA damage as experimental anticarcinogens. A list is displayed in Appendix A, and includes phenols and drugs that inhibit arachidonic acid metabolism, but does not specifically address NDGA.

Cancer development in humans proceeds through the stages of initiation, promotion and progression. Anticarcinogens, antitumorigenic agents and cancer inhibitors function in a number of ways to influence the development of cancer in humans. Nutritional anticarcinogens found in functional foods may (1) inhibit tumor initiation by altering cellular functions, (2) sequester active forms of carcinogens and prevent them from reaching target sites, (3) enhance the body's defense system, (4) inhibit or reduce progression of cancers, and/or (4) prevent the activation of genes and the proliferation of cells by tumor promoters. (VERIS Research Summary, 1999; Johnson, 1997; Bailey & Williams, 1993). Antioxidants in various amounts function as cancer inhibitors, but may also function as promoters in large doses or in certain cancers. "Conversely, a dietary deficiency of the antioxidants may enhance the incidence of certain cancers." (VERIS Research Summary, 1999, pg.2).

The association of dietary intake of fat and fatty acids with breast cancer is particularly germane to this research. NDGA is a potent antioxidant preservative for natural fats, i.e., lard from animal fat, and was used in the United State from 1942 to 1968. NDGA continues to be utilized as a fat antioxidant in twenty countries, some of which import lard and fat products from the United States (Jahhav, Nimbalkar, Kulkarni & Madhavi, 1996; Leatherhead Food Research Association, Foodline®: Current Food Legislation, 2001)

Large-scale health related studies on food, antioxidants, other phytochemicals and breast cancer have been conducted, and some are on going. The following list identifies some of the major studies, with a brief synopsis of the magnitude of the study.

1. Woman's Health Initiative (WHI), funded by the National Institutes of Health (NIH) and administered by the National Heart, Lung, and Blood Institute (NHLBI); a 15 year study, started in 1991, to end in 2006; 160,000 women, 50 to 79 years of age, conducted in 45 clinical centers; frequently referred to as the Women's Health Study. (NIH News Release, 1998). The study is designed to answer common questions about the use of hormone replacement therapy, calcium supplements, and diet in the prevention and treatment of heart disease, osteoporosis, and breast and colorectal cancer. (National Institutes of Health, N.R., 1998).
2. The European Community Multicentric Study on Antioxidants, Myocardial Infarction, and Cancer of the Breast (EURAMIC), a multi-national case-control study was conducted between 1990 and 1992. The study involved sites in the United States, the Netherlands, Northern Ireland, Spain, Switerzland, Germany and Finland. Participating countries financed it as a concerted action by the Commission of European Countries. One purpose of the study was to examine potential protective roles of antioxidants in the development of breast cancer. (Kohlmeier & Mendez, 1997).
3. National Cancer Institute's Beta Carotene and Retinol Efficacy Trial (CARET), begin in 1996 and stopped early (after 4 years) due to evidence suggestive that above normal doses of beta carotene acted as promoters of lung cancer rather than inhibitors. (Omenn, Goodman, Thornquist, Balmes, Glass, et al., 2000)
4. The Supplementation with Vitamins and Minerals Antioxidants (SU.VI.MAX) study is primary prevention trial designed to test the efficacy of daily supplementation with antioxidant vitams and minerals at nutritional doses, in reducing the frequency of major health problems in industrialized countries, especially cancers and cardiovascular deaths. The study involves 12, 735 eligible subjects. It began in 1994 and ends in 2002 (Hercberg, Galan, Preziosi, Roussel, Arnaud, Richard, et al., 1998) (http:verlag.hanshuber.ch/Zeitschriften/IJVNR/98/vn9801.html)

In addition, the following large-scale studies on breast cancer specifically, have produced volumes of literature on nutritional substances, nutrients, functional foods, phytochemicals, and other biologically active compounds in food, which affect the initiation, promotion, and progression of cancers.

1. New York Women's Health Study (NYU Women's Health Study): is a prospective cohort study began in 1985 with the collaboration of the Guttman Institute; over 15,000 women from New York City and Florida have enrolled; goal is to identify the role of endogenous hormones, diet, and other environmental exposures in the etiology of most common cancers in women, especially breast cancer. (Community Advisory Committee of the Women's Health Study, 1998)
2. Nurse's Health Study: a cohort study started in 1976, had a total of 88, 795 women free of cancer in 1980 and followed up for 14 years. (Holmes, Hunter, Colditz, Stampfer, Hankinson, Speizer, Rosner, & Willett, 1999).

3. Canadian National Breast Screening Study (NBSS): This study began in January 1980, with women aged 50–59 years. The results reported in September, 2000 were: "In women aged 50-59 years, the addition of annual mammography screening to physical examination has no impact on breast cancer mortality." (Miller, To, Baines and Wall, 2000, pg. 1).

Controversy continues in regards to diet and breast cancer, despite numerous research studies. Kohlemier and Mendez, writing in *Proceedings of the Nutrition Society* have clearly, insightfully, and dramatically summarized the current knowledge and belief in the area of food-borne exposures and breast cancer. They explore the major studies on dietary fat, antioxidants, cruciferous vegetables, xeno-oestrogens, and alcohol as they relate to human breast cancer. Relationships in all categories are present. However given the limitations of the studies, no strong associations are found. These researchers raise the quintessential question for prevention: Is there any reason to believe the factors associated with breast cancer appearance in adulthood, are the causative agents? And in conclusion, they acknowledge, "the potential for diet to reduce recurrence of breast cancer is thoroughly understudied." (Kohlemier & Mendez, 1997, p.379).

Epidemiological and ecological studies of functional foods and breast cancer are abundant (Toniolo, Riboli, Shore & Pasternack, 1994; Simonsen, van't Veer and Strain, 1998; Holmes, et.al, 1999). These epidemiological studies have not been followed-up with large scale biological, *in vivo*, controlled studies or even by careful analysis of the *in vitro* cellular and animal studies with induced and spontaneous breast cancers. However significant progress continues to be made in defining for understanding the relationship of dietary factors and nutrients to carcinogenesis (National Cancer Institute {NCI}, Division of Cancer Prevention and Control [DCPC], 1994). Multidisciplinary "research on the cellular and molecular regulation relevant to nutrition and cancer" (NCI, DCPC, 1994) will further the identification of a chemopreventative agent for human breast cancer.

The National Cancer Institute (NCI) has an established research agenda for breast cancer prevention studies, based primarily on evidence that the development of the disease is linked to exposure to the hormone estrogen (NCI, 1999b). In 1992, NCI funded the Breast Cancer Prevention Trial (BCPT), which demonstrated a "49 percent fewer diagnoses of invasive breast cancer in women who were randomized to take tamoxifen, a SERM [selective estrogen receptor modulators] compared with women who were randomized to take a placebo…Women on tamoxifen also had 50 percent fewer diagnoses of noninvasive breast tumors, such as ductal or lobular carcinoma in situ." (NCI, 1999a, pg.1). Another NCI prevention study, STAR (Study of Tamoxifen and Raloxifene) began recruiting participants in June 1999 at more than 400 centers across the United States, Puerto Rico and Canada. This trial is designed to find out whether raloxifene, an anti-osteoporosis drug, is as effective in reducing the chance of developing breast cancer as tamoxifen, and to compare the side effects of the two agents (NCI, 1999b). However, estrogen is only one factor that increases the relative risk for breast cancer in women. The American Cancer Society (ACS) list includes 26 other risk factors. The relative risk of those factors is displayed in Table F.

[Note: A relative risk compares the risk of disease among people with a particular exposure to the risk among people without the exposure. If the relative risk is above 1.0, then risk is higher among exposed than unexposed persons.] (American Cancer Society, 2000).

Relative Risk	**Factor**
Relative Risk >4.0	Inherited genetic mutations for breast cancer
	Age (65+ v. <65 years, although risk increases across all ages until age 80)
	Two or mor first-degree relatives with breast cancer diagnosed at an early age
	Personal history of breast cancer

Relative Risk	Factor
Relative Risk 2.1 – 4.0	Nodular densities on mammogram (>75% of breast volume) One first-degree relative with breast cancer Atypical hyperplasia High-dose ionizing radiation to the chest Ovaries not surgically removed <age 40
Relative Risk 1.1 2.0	High socioeconomic status Urban residence Northern US residence White (for breast cancer diagnosed after age 45) Black (for breast cancer diagnosed before age 40) Never married Late age at first full-term pregnancy (>30 years) No full-term pregnancies (for breast cancer diagnosed at age 40+ years) Early menarche (<12 years) Late menopause (>55 years) Recent oral contraceptive use Recent hormone replacement therapy Alcohol consumption (2 to 3 drinks, or more, per day) Postmenopausal obesity Tall Personal history of cancer of endometrium, ovary, or colon Never breast fed a child Jewish heritage

Table F: Factors that Increase the Relative Risk for Breast Cancer in Women.

This extensive listing of risk factors dramatically emphases the 'wilderness searching' taking place in breast cancer research.

However, a persistent link has been demonstrated between dietary fiber intake, estrogen levels and breast cancer in women. In addition, a preventative role for the phenolic antioxidant nordihydroguaiaretic acid is readily apparent in the biophysiological processes of ingestion, digestion, absorption and assimilation of dietary fiber. When dietary fiber is discussed, the term 'lignin' is conjured. Closely related to lignins, is the plant phenolic compound, the 'lignans'. Lignans are widely spread throughout the plant kingdom, functioning primarily as defenders against plant pathogens (i.e., alleopathic characteristics) or acting as antioxidants in flowers,

seeds, seed coats, stems, nuts, bark, leaves, and roots (Gisvold, 1974; Croteau, R., Kutchan, T., & Lewis, N., 2000). (The alleopathic characteristic of NDGA has been described in earlier sections). Dietary plant lignans have health-protecting functions. The lignan may be ingested as part of a plant or synthesized by intestinal bacteria from specific insoluble components of grains and other fiber-rich foods (Jones, Gonzales, Pillow, Gomez-Garza, Foreman, Chilton, et al., 1997; Aldercreutz, H., 1998;). These ingested or synthesized mammalian lignans undergo "enterohepatic circulation, in which they are conjugated in the liver, excreted in the bile, deconjugated in the intestine by bacterial enzymes, absorbed across the intestinal muscosa, and returned to the liver in the portal circulation" (Croteau, R., Kutchen, T.& Lewis, N., 2000, p.1296). Ingested as the phenolics secoisolariciresinol and matairesinol, they are converted to enterodiol and enterolactone, which are believed to be chemopreventative for breast and prostrate cancer (Croteau, R., Kutchen, T. & Lewis, N., 2000; Aldercreutz, H., 2001; Heinonen, S., Nurmi, T, Liukkonen, et al., 2001; Aldercreutz, H, 2002). The hypothesized mechanism is via increased binding of circulating estrogens to serum proteins, which causes a reduction in their enterohepatic circulation.

CHAPTER III

METHODOLOGY

Emulating the methodology described extensively by D.R. Swanson (1986b, 1987, 1988, 1990a, & 1991; Swanson & Smalheiser, 1996, 1997 & 1999), a logical argument and syllogistic model for research on the literatures of functional foods, nordihydroguaiaretic acid (NDGA) and breast cancer is presented. The generic research question is: "Can solutions to problems in one discipline be found in the literature of another discipline by finding unrecognized links between the literatures of the two disciplines?" This study asks the question: " Does there exist a possible preventative relationship between breast cancer, and nordihydroguaiaretic acid (NDGA), a phytochemical antioxidant and potential functional food? ". A mapping of the scientific literature on the role of functional foods, NDGA as an anticarcinogenic agent and the status of breast cancer will be performed, following the steps and procedures described by D. R. Swanson.

The specific research questions in the study are as follows:

1. Will cocitation analysis of the public literature on functional foods and nordihydroguaiaretic acid, exclusive of the breast cancer literature, reveal undiscovered connections?
2. Will cocitation analysis of the public literature on functional foods and nordihydroguaiaretic acid, exclusive of the breast cancer literature, reveal linkages of a possible preventative agent?
3. Will cocitation analysis of the public literature on nordihydroguaiaretic acid and the public literature on breast cancer, reveal undiscovered connections?

4. Will cocitation analysis of the public literature on nordihydroguaiaretic acid and the public literature on breast cancer, reveal linkages of a possible preventative agent?
5. Will cocitation analysis of the public literature on functional foods and nordihydroguaiaretic acid and the public literature on breast cancer, reveal undiscovered connections?
6. Will cocitation analysis of the public literature on functional foods and nordihydroguaiaretic acid and the public literature on breast cancer, reveal linkages of a possible preventative agent?

Research Design

This is a replication study; therefore, the paradigmatic syllogism will follow the phase 1 approach as described and used in Swanson's work. The syllogism is as follows:

A = Functional foods literature [as nutritional anticarcinogens].

B = NDGA literature [as an antioxidant and anticarcinogenic agent].

C = Breast cancer literature [prevention of].

thus:

A relates to/effects B = AB. In other words: $A \cap B$.

B relates to/effects C = BC. In other words: $B \cap C$.

if A relates to B, and AB effects C = (A intersection B) intersection C = ABC. In other words: $(A \cap B) \cap C$.

Stated as formal hypotheses, the research questions were as follows:

H_1: In the syllogistic paradigm of A intersection B, a literature search of the human and animal cell research with nordihydroguaiaretic acid will establish characteristics of nordihydroguaiaretic acid shared with functional foods.

H_2: In the syllogistic paradigm of B intersection C, a cocitation analysis of the nordihydroguaiaretic acid *in vivo* research literature and the breast cancer literature will reveal an absence of linkages, therefore disjointness of the literatures.

H_3: In the syllogistic paradigm of A intersection B intersection C, an undiscovered public knowledge phenomena will be explicated, i.e., nordihydroguairetic acid is chemopreventative for breast cancer.

Determining the choice of keywords (i.e., key terms, phrases or terms) to be utilized in the literature searches was essential. The establishment of a risk-reduction relationship, i.e., prevention, between functional foods such as NDGA, and breast cancer is dependent on an exhaustive search of the sets of literature. Therefore, several techniques have been utilized to identify keywords. First, an exhaustive preliminary search for the involved terminology and definitional terms was conducted, beginning with NDGA documents from 1897 to 2001. Second, experts in searching the literature in the areas of nutritional/dietary sciences and human cancer were consulted to verify the validity of the keywords as measurement devices of the risk-reduction relationship. Third, in June 2001 a pilot study was conducted to establish the validity of the searching keywords. Forth, a taxonomy for NDGA was developed. Synonyms and definitional terms were developed for functional foods, and modifers for breast cancer/breast neoplasm were refined. The following sections elaborate on the four techniques for identifying the keywords to be used in the searches.

Preliminary Keyword Searches

The search for keywords to conduct combinatorial searching was exhaustive. Changes have occurred over time in the choice of terms, as well as the introduction of new terms and variations in spelling. The controlled vocabulary in PubMed® (PubMed), an online bibliographic database (® National Center for Biotechnology Information [NCBI] at the National Library of Medicine

[NLM], Bethesda, MD, www.pubmed.gov) was consulted for possible categories or subheadings, and provided the basis for exclusion of some closely related but limiting, older terms. Variations on spelling of the phytochemical NDGA and the use of synonyms in different medical specialties were accounted for when deciding on search terms to include for NDGA. Nordihydroguaiaretic acid is the preferred term for NDGA, while a variation in spelling of nordihydroguiaretic acid occurs in limited circumstances. These spellings are the most common in biomedical research, with one exception. The specialty of dermatology prefers the term 'masoprocol' or 'actinex'. Both terms were searched and no documents related to breast cancer or functional foods were retrieved. In addition, neither the chemical abstract number (CA) nor the chemical registration number (RN) was included. Extensive searching of the NDGA literature demonstrated these chemical designations are used by chemical companies, and not by biomedical research specialists.

The term 'functional foods' does not have an official definition in the United States, although several are presented in the literature. Therefore most related terms were searched, inclusive of those used interchangeably in the food science, agriculture, nutrition and business, and alternative and complementary therapies literature. These terms were selected after examining 82 journals indexed by PubMed and the 83 journal titles not included in PubMed, but listed in the Food Science and Nutrition Journals of Science website, renamed MedBioWorld at: http://www.medbioworld.com/ bio/journals/ food.html

Consultation with Experts

The second step in refining the search terms was to consult with an expert in dietary science and a medical librarian. The functional food terms were reviewed and approved by Dr. Jane Dennis, Department Head, Human Sciences, Tarleton State University, Stephenville, Texas.

Some related terms were excluded. Common terms such as 'whole', 'fortified', 'enriched' or 'enhanced' foods were not included. These are older terms from controlled vocabularies, which refer to a process of adding traditional nutrients to foods not normally having these substances.

The medical research librarian at the National Institutes of Health (NIH) conducted a test of the terms used in CANCERLIT® (CANCERLIT), a bibliographical cancer database (® U.S. National Cancer Institute [NC], National Library of Medicine [NLM], Bethesda, MD). The librarian's search was then replicated with a search on BIOSIS Previews® (BIOSIS Previews), a biological and biomedical sciences database (® Biological Abstracts Inc. [BIOSIS®], Philadelphia, PA). The results of the BIOSIS Previews search included the same documents with several additions. The term 'breast neoplasm' is a MeSH term in the controlled vocabulary of PubMed, and documents retrieved were cross-referenced with 'breast cancer'. Therefore, 'breast cancer' was the primary term for searching in all the databases, and 'breast neoplasm' was the secondary term.

Pilot Study

The next step was to determine the number of possible existing documents related to functional foods, nordihydroguaiaretic acid and breast cancer. Using the preliminary searching keywords, a pilot study was conducted in June 2001. The goal of the pilot study was to identify the number of documents published in a limited time period, from 1996 – June 2001. The pilot study was conducted on seven databases and they are described below.

1. PubMed: This National Library of Medicine database includes MEDLINE, PreMEDLINE and HealthStar journal citations. PubMed covers 1966 to 2001.
2. BIOSIS Previews: This database covers Biological Abstracts/Reports, Reviews and Meeting (BA/RPM) with content related to the biological and biomedical sciences. File

#5 in this database covers 1969 to 2001.

3. EMBASE ® (EMBASE), a human medicine and related disciplines database (® Elsevier Science B.V., New York, NY) covers human medicine and related disciplines. File #73 covers 1973 to 2001.
4. CANCERLIT, is a cancer bibliographic database produced by the International Cancer Research Database Branch (ICRDB) of the United States National Cancer Institute. File # 159 covers 1963 to 2001.
5. CAB HEALTH® (CAB HEALTH), a combination database (® combines CAB ABSTRACTS, a human health and disease-related information database and a file from Public Health and Tropical Medicine database, Commonwealth Agricultural Bureau International [CABI] Publishing, Wallington, Oxon, U.K.) combines resources on human health, public health and diseases-related information. File # 162 covers 1973 to 2001.
6. Foodline®: Food Science and Technology, (Foodline), a food science and technology database (® Leatherhead Food Research Association, Leatherhead, Surrey, U.K.) covers all aspects of the the food and drink industry. File # 53 covers 1972 to 2001.
7. IBIDS, the International Bibliographic Information on Dietary Supplements Database, is a public service database. It is a collaborative database developed by the National Institutes of Health and the United State Department of Agriculture. IBIDS may be accessed at www.nal.usda.gov/fnic/IBIDS/ . IBIDS covers 1986 to 2001.

The numbers of documents retrieved in the pilot study are shown in Table G.

Documents Retrieved in Databases From 1996 to 2001	
Keywords	Total Number of Documents Retrieved From Seven Databases
1. NDGA	370
2. Functional foods	3036
3. NDGA and functional foods	0
4. NDGA and breast cancer	20
5. NDGA and breast neoplasms	0
6. NDGA and phytochemicals	2
7. NDGA, breast cancer & functional foods	0
8. Lipoxygenase inhibitors & breast cancer	11
9. Phytochemicals & breast cancer	47
10.Medical foods & breast cancer	2
11.Chemopreventative agents & breast cancer	4
12. Nutraceuticals& breast cancer	1
13. Breast cancer & functional foods	23
14. Breast neoplasms & functional foods	14
Total	3669

Table G: Number of Documents Matching Keyterms in Databases Searched in the Pilot Study

The total number of documents retrieved was 3669. The pilot study revealed a significant finding in that the search of IBIDS, a dietary supplements database which includes functional foods, retrieved a total of 357 articles related to either NDGA or breast cancer or both, in the five year period searched.

An example of the technique used in the pilot study can be found in Appendix E. The document was retrieved searching BIOSIS Previews using the terms phytochemical and breast cancer. Assessments of the results of the pilot study are as follows:

1. The databases were specialized, therefore some of the journals were not covered in every database. PubMed, BIOSIS Previews and EMBASE databases covered

similar content, whereas CANCERLIT was more restricted to cancer related content. Likewise, Foodline covered food, dietary science and the food service industry and IBIDS covered dietary supplements. CAB HEALTH covered human health and disease-related information.

2. Database structure restricts retrieval; therefore 'command search'should be used in DialogWeb, and 'advance search' on some of the other databases.
3. All possible relevant definitional terms should be searched; however, non-essential terms should not be used, e.g., 'primary' with breast cancer.
4. PubMed mapping limits retrieval in menu driven searches therefore use the 'advance search' techniques.
5. There exists a large body of literature related to functional foods, NDGA and breast cancer.

The searching for documents in the databases to establish a possible link in a knowledge synthesis paradigm required extensive cross-reference searching. The ultimate aim was to demonstrate the *absence* of linkages between two literatures that are logically and scientifically related, and to construct a reasonable argument supporting the need for new research based on the uncovered knowledge synthesis. The search profile was formulated from knowledge of terminologies, characteristics of scientific publications, and database features. And, in the case of organic substances, knowledge of the biological action of the substances being investigated was crucial for sustaining authenticity. This research endeavor covered a span of twenty-two years; therefore, adjustments were necessary to accommodate new terms or phrases, new knowledge discoveries, and changes in database configurations.

The primary focus of this study was to determine if NDGA has been researched as a functional food chemopreventive agent for breast cancer in humans. The search and retrieval method used was combinatorial, keyword searching of databases. In this method, the selected keywords were used in combination with 'functional foods', 'nordihydroguaiaretic acid', and 'breast cancer' for a combinatorial technique. For example, 'food additive' was combined with 'nordihydroguaiaretic acid' and a search was conducted to identify documents using both terms. With combinatorial, keyword searching, the number of documents retrieved were reduced. When seeking to establish a conceptual front or discipline linkage, the starting effort is the most difficult. Combinatorial, keyword searching (1) identified the authors in the disciplines; (2) limited document retrieval to more obviously relevant documents; and (3) allowed for verification of each citing document. The structure for this study required precise definitions and classifications in order to make the logical connections between functional foods, NDGA research and breast cancer prevention. Keyword searches retrieved numerous documents, both from controlled vocabulary databases such as PubMed, and subject oriented databases such as BIOSIS Previews, EMBASE, CANCERLIT, and specialty databases such as CAB Health, Foodline: Food Science and Technology, and IBIDS. Based on the results of the previously described steps to identify keywords, a taxonomy for NDGA was developed, synonyms and definitional terms were identified for functional foods, and modifiers for breast cancer/breast neoplasm were refined. This was done in order to accurately place the subject matter in a searchable context and assist in refining combinatorial keywords. For the last nine years, this researcher searched the literature on NDGA and conducted analysis of specific characteristics of NDGA. Based on expert opinion and search expertise, the two sets of literature (the target and source literatures) were searched on approved terms. The terms were selected based on the

purpose of the research and with the intent of being exhaustive. The search terms for the literatures of NDGA and of breast cancer prevention were selected for exactness and specificity. However the search terms required for functional foods included broader, survey-type terms, as this is a relatively new, expanding field of science and without complete acceptance of a definitional base. In the following sections more detailed explanation is presented of the NDGA taxonomy, functional foods definitional base and the breast cancer prevention search terms.

NDGA Taxonomy

The taxonomy for the plant *Larrea tridentata* that produces nordihydroguaiaretic acid (NDGA) was complied from plant research dating from 1897 through 2002. The characteristics and functions of NDGA were analyzed using 1816 documents reported in PubMed from 1980 to May 2002. The following condensed botanical taxonomy from Croteau, Kutchan & Lewis (2000), USDA, Natural Resources Conservation Service (1997), McAuliffe (l994), Downum (1988) and Botkin (1949) was utilized in this project.

1. Family: Zygophyllaceae
2. Genus: Larrea
3. Species: tridentata
4. Common name: creosote bush
5. Natural product class: lignan
6. Functions: polyphenolic antioxidant, 5-lipoxygenase inhibitor, arachnoidic acid inhibitor, anti-inflammatory, anticarcinogenic, antitumorigenic, antimutagenic, antigenotoxic, chemopreventive agent.

NDGA is considered a non-food substance, rather an herbal or medicinal extract or a botanical. It was used in the food industry until 1968, at which time it was replaced by cheaper,

synthetic chemical antioxidants. As a result of this displacement and no further food-related research, it was placed on the FDA 'banned ' status. A focus of the study was to establish NDGA as a potential 'functional food' because of (1) shared characteristics with secondary metabolites (which are a primary focus of functional foods) and (2) the extensive laboratory research describing the biochemistry and biomolecular attributes of this phytochemical, which have been elucidated in the literature review.

Based on the taxonomy and the attributes of NDGA as previously described, search terms for NDGA were refined to include only terms that clearly define NDGA and its neoplastic chemopreventive characteristics as related to breast cancer, rather than all the functions of NDGA, which are numerous and would retrieve extraneous documents. The pilot study did not retrieve any documents with the two terms 'nordihydroguaiaretic acid' and 'functional foods'. Significantly, an expanded search of the seven databases with the two terms did not retrieve any documents with 'nordihydroguaiaretic acid' and 'functional foods'. The keyword 'phytopharmacognacy' was included to explore for any reference in this new field of science on plant pharmacology. To establish the status of NDGA as chemopreventive for breast cancer, the following terms were used in the combinatorial searches:

	Search Terms
1.	Anticarcinogen
2.	Antioxidant
3.	Antitumorigenic
4.	Antimutagen
5.	Chemopreventative
6.	Chemopreventive
7.	Phytopharmacognacy
8.	*in vivo*

TABLE H: List of Search Terms Combined with NDGA.

In addition, for possible retrieval of other documents with human *in vivo* research, the term nordihydroguaiaretic acid was combined with the search terms (1) 'breast cell line', (2) 'cell

line', (3)'cell lines' and (4) '*in vivo'* in order to identify NDGA research in the general breast cancer literature. The result of these searches was to substantiate the lack of human breast cancer search with NDGA. The results are reported in Table S in Chapter IV. The following terms were eliminated: phytonutrients, phytochemicals, flavonoids, isoflavones, phenols, phytoestrogens, probiotic. These terms are too general in scope or describe broad functional qualities. For example, the lignans such as NDGA are only one of the phytoestrogens - others are isoflavones, coumestanes, fungoestrogens and resorcylic acid lactones.

Functional Foods Definitional Base

In order to understand functional foods and the connection to NDGA, further explanation of the position of functional foods in the food chain is provided. The plant biologists discuss eatable plants in two categories, primary metabolites and secondary metabolites [or 'natural products'] more on the basis of function, rather than a strict taxonomy. Three reasons for this division is explained in Croteau, Kutchen & Lewis (2000) as the following: (1) terminology relates to function; (2) research on secondary metabolites has only begun to extend to the depths needed to make accurate classification; and (3) there is an obvious overlapping of functions between categories e.g., phenols and flavonoids.

Primary metabolites are those substances that plants require to sustain themselves. They are frequently the primary nutrients and chemicals required by the human body. Secondary metabolites are plant-produced substances for defense, enhancement of propagation, establishing flower color, and contributing to certain flavors and odors, i.e., influencing the ecological interactions between the plant and its environment (Croteau, Kutchan, & Lewis, 2000). These secondary metabolites are the source of many functional foods and may have medicinal value.

The plant biologists, Cruteau, Kutchen & Lewis poignantly illustrates the connection between functional foods, lignans (e.g., NDGA) and preventive medicine as following:

> "Advances in lignan and (iso) flavonoids biochemistry and molecular biology offer the opportunity to modify concentrations of health protectants and pharmacologically active species in particular plants of choice. Eventually, we should be able to engineer the formation of secoisolariciresinol, matairesinol, daidzein, genistein and similar compounds in staple crops that do not ordinarily produce them in significant quantities. The corresponding transgenic plants thus would provide long-term health benefits as sources of cancer prevention." (Croteau, Kutchan & Lewis, 2000, p 1314)

NDGA is one of the secondary metabolites from the *Larrea tridentata* plant, commonly known as creosote bush. It has discrete bioactivities toward mammalian biochemistry and metabolism, and could be added to the food supply via food-processing technology. NDGA is potentially chemopreventive for breast cancer (and other types of cancer) from four aspects: (1) the antioxidant properties which prevent free radical damage to DNA (Harper, Kerr, Gescher & Chipman, 1999; Nakayama, Hori, Osawa & Kaawaskishi, 1992); (2) the lipoxygenase and (3) eicosanoid synthesis inhibitor properties suppress tumorigenesis and tumor cell proliferation and induce apoptosis (Seufferlein, Seckl, Schwarz, Beil, Baust, Luehrs, et al., 2002; Noguchi, Earashi & Miyazaki, 1995; McCormick, 1987); and (4) the phytoestrogenic lignan properties are protective for breast and colon cancer (McCann, Muti, Trevisan, Vito, Ram & Freudenheim, 2002; Pietinen, Stumpf, Mannisto, Kataja, Uusitupa & Adlercreutz, 2001; Park, 1998; Adlercreutz, 1992;).

The connection from functional foods to breast cancer is related to estrogen. Breast cancers are considered estrogen-receptor-positive or estrogen-receptor-negative, depending upon their type of receptor-sites and their response, i.e., proliferation, from endogenous estrogen stimulation. From one-third to two-thirds of all breast cancers have estrogen receptors and depend on estrogen for growth. Anti-estrogens can block the binding of estrogen to its receptor, thus preventing estrogen from stimulating breast tumor cell division and multiplication. Functional foods can be estrogen blockers. For example lignans and isoflavonoid phytoestrogens affect hormone metabolism and production and cancer cell growth in many different mechanisms, one of which is sex hormone binding by proteins, thus lowering the serum level of the circulating hormones (Adlercreutz, 1992).

Another pathway by which lignans affect cancer cell growth is by competitive inhibition. When the plant lignans secoisolariciresinol and matairesinol are ingested into the gastrointestinal system they are converted *in vivo* to enterodiol and enterolactone, which have estrogenic and antiestrogenic activities and have a competitive inhibition effect on endogenous estrogens (McCann, et al., 2002; Meagher & Beecher, 2000), thus they are probably chemopreventive. The cocitation analysis of functional foods and NDGA and breast cancer in this study was restricted to the antioxidant and lignan-related antiestrogenic competitive inhibition action of NDGA, as a preventive for breast cancer.

The functional classification of primary and secondary plant metabolites is presented in Table I, to substantiate the estrogenic-related terms used in this study. Also Table I identifies commonly recognized foods or food components, which are either primary or secondary plant metabolites. The very broad discipline of plant biology and plant biology research connects with

several other significant disciplines, i.e., genetics, biomedicine, nutrition, agriculture. All of these disciplines are closely related to functional foods, NDGA and breast cancer prevention.

PRIMARY METABOLITES	SECONDARY METABOLITES
1. phytosterols • e.g., stanol esters in corn, soy, wheat	1. terpenoids (25,000+) • e.g., plant lipids
2. acyl lipids, o e.g., lipids involved in photosynthesis	2. .alkaloids (12,000+) • e.g., organic nitrogenous bases, including atropine, caffeine, morphine, nicotine
3. nucleotides, • e.g., building blocks of nucleic acids (DNA;RNA)	3. phenylpropanoids and allied phenolic compounds (8,000+): • flavonoids (in tea, fruits, citrus) o isoflavonids • lignans (in rye, flax, NDGA) • lignins (cellulose) • sinapic esters o includes acids, such as in mustard seeds
4. amino acids, e.g., building blocks for proteins	
5. organic acids, • eg., phenolic compounds & acids madeup of molecules containing organic radicals (acetic acid; citric acid)	

TABLE I: Primary Metabolites and Secondary Metabolites in Plants, Related to Estrogenic Actitivity.

The term *functional foods* covers several classifications of products currently marketed. These include, but are not limited to fortified foods, dietary supplements, nutraceuticals, botanical and herbal supplements. Although several definitions of *functional foods* have been discussed in the nutrition and dietary science literature, the emerging acceptable definition which is supported by the International Foods Information Council Foundation (IFIC) is: "Any food which provides health benefits beyond basic nutrition." (International Food Information Council [IFIC] Foundation, 2002). Several classes of primary metabolites and secondary metabolites are being promoted, consumed, and researched as providing health benefits beyond basic nutrition.

Therefore, the search terms for functional foods included a set of definitional synonyms and a set of other related terms. The functional food search terms are listed in the following Table J:

Search Terms
1. cosmeceuticals
2. food additives
3. designer foods
4. genetic foods
5. genetically engineered foods
6. medicinal foods
7. nutraceuticals
8. pharmafoods
9. therapeutic foods
10. lignans
11. prebiotics

TABLE J: Functional Foods Search Terms

The search terms for functional foods includes nine terms that are synonyms and two terms that are descriptive of classes of functional foods. The term 'lignan' refers to specific functional foods, as does the term 'prebiotic'. 'Lignans' and 'prebiotics' also relate to NDGA. Lignans are metabolized by human fecal microflora. A 'prebiotic' is a nonviable food ingredient seen as beneficial to the host and which is selectively metabolized by intestinal species (Roberfroid, 1998; Adlercreutz, 2001; Gibson, 2002). 'Lignans' and 'prebiotics' are considered *functional foods*.

Breast Cancer Search Terms

Breast cancer terms were selected from the controlled vocabulary of PubMed, and the searches performed by a library specialist in the database CANCERLIT. While the PubMed controlled vocabulary allows the use of the terms 'breast cancer' or 'breast neoplasm', the more commonly accepted term in other databases was 'breast cancer'. Table K identifies search terms for breast cancer.

Search Terms
1. Breast cancer
2. Breast neoplasm

TABLE K: Breast Cancer Search Terms

A content focus of this study is 'breast cancer', 'breast neoplasm' and the prevention of breast cancer. In the database searches the keywords for functional foods and NDGA are combined with breast cancer and breast neoplasm for combinatorial keyword searches. Therefore these sets of keywords function as limiters to restrict document retrievals to a prevention focus. The broad topic of breast cancer prevention was not a specific search area for this study. The goal was to search for a specific chemopreventative agent. In order to differentiate the search parameters, an investigative search was conducted and produced the following results:

NDGA & BREAST CANCER Prevention Search Terms	**DATABASES**						
	PubMed	**BIOSIS**	**EMBASE**	**CANCERLIT**	**CAB Health**	**Food Sci/Tech**	**IBIDS**
1. NDGA AND breast cancer AND prevention	3	0	1	0	0	0	3
2. Breast cancer AND Prevention	7313	1340	6534	42	194	98	1003
3. Breast cancer prevention	472	27	0	0	0	0	1003

Table L: NDGA and Breast Cancer Prevention

The terms 'nordihydroguiaretic acid' and 'breast cancer' and 'prevention' retrieved seven documents, three of which were unique. The authors of the unique documents were: Schultze-Mosgau, Noguchi, and Sathyamoorthy. These three authors documents were previously retrieved and are in the author cocitation analysis for NDGA and breast cancer. The search results substantiate the limiters authenticity for searches on NDGA and breast cancer prevention. The other documents are in three general catagories: (1) review articles; (2) documents on tamoxifen and new, unapproved drugs; and (3) cultural and personal perspectives on breast cancer and breast cancer prevention.

A number of restrictive terms for breast cancer were eliminated from the originally considered search terms, including: (1) human; (2) female; (3) mammary neoplasms; (4) neoplasms by site and /or tissue diagnoses; (5) neoplasms, experimental. These terms restricted the search and eliminated the retrieval of some documents related to the prevention of breast cancer. General terms were eliminated if they described broad classes of substances in addition to NDGA and/or functional foods and/or were related to general breast cancer research. These included: phytochemical(s), phytonutrients, phenols, flavonoids, isoflavones, phytoestrogens, probiotics, etiology, epidemiology, and pharmacology.

The next database searches were combinatorial searches with all terms for the target literature (functional foods and nordihydroguairetic acid) and the source literature (breast cancer). For instance, "nordihydroguaiaretic acid" AND "breast cancer" were combined with all search terms listed in Table H, Table J and Table K. The database searches were configured within the structure and characteristics of the database, with documents limited to (a) English and (b) the years 1980 through May 2002. The PubMed database was searched using the 'advance search'. Using DialogWeb, the databases of BIOSIS Previews, EMBASE, CANCERLIT, CAB HEALTH and Foodline: Food Science and Technology were searched using 'command search'. IBIDS was searched using the menu driven 'keyword search'. Now that the techniques for establishing a reliable searching vocabulary have been described, the steps in the methodology follow.

Steps of the Methodology

The methodology consisted of electronic database searches of two different sets of literature, the target literatures and the source literatures. The target literatures are the functional foods and NDGA literatures. The source literature is the breast cancer literature. The search services

utilized were DialogWeb, the National Library of Medicine, and the National Agriculture Library. The databases searched were: PubMed, BIOSIS Previews, EMBASE, CANCERLIT, CAB HEALTH, Foodline: Food Science and Technology and IBIDS. As a reminder the research questions were:

1. Will cocitation analysis of the public literature on functional foods and nordihydroguaiaretic acid, exclusive of the breast cancer literature, reveal undiscovered connections?
2. Will cocitation analysis of the public literature on functional foods and nordihydroguaiaretic acid, exclusive of the breast cancer literature, reveal linkages of a possible preventative agent?
3. Will cocitation analysis of the public literature on nordihydroguaiaretic acid and the public literature on breast cancer, reveal undiscovered connections?
4. Will cocitation analysis of the public literature on nordihydroguaiaretic acid and the public literature on breast cancer, reveal linkages of a possible preventative agent?
5. Will cocitation analysis of the public literature on functional foods and nordihydroguaiaretic acid and the public literature on breast cancer, reveal undiscovered connections?
6. Will cocitation analysis of the public literature on functional foods and nordihydroguaiaretic acid and the public literature on breast cancer, reveal linkages of a possible preventative agent?

The methodological steps for researching the six questions are listed below. The paradigmatic syllogism designates the following sequencing for the literatures:

A = Functional foods literature [as nutritional anticarcinogens].

B = NDGA literature [as an antioxidant and anticarcinogenic agent].

C = Breast cancer literature [prevention of].

Step 1: Searched databases for documents.

The following databases were searched:

1. PubMed via the National Library of Medicine.
2. BIOSIS Previews, EMBASE, CANCERLIT, CAB HEALTH and Foodline via DialogWeb.
3. IBIDS via the National Agriculture Library.

These databases were searched using combinatorial keywords for functional foods, nordihydroguaiaretic acid and breast cancer/breast neoplasm. For the purpose of reporting the search strageties performed, the following acronyms are used:

- ***FFK*** is used for functional food keywords: cosmeceuticals, food additives, designer foods, genetic foods, genetically engineered foods, medicinal foods, nutraceuticals, pharmafoods, therapeutic foods, lignans, prebiotics.
- ***NAK*** is used for nordihydroguaiaretic acid keywords: anticarcinogen, antioxidant, antimutagen, antitumorigenic, chemopreventative and chemopreventive agent, phytopharmacognacy and *in vivo*.
- ***BrCaK*** is used for breast cancer/breast neoplasm keywords: breast cancer, breast neoplasm.

To address the research questions the following search strageties were used to search the databases listed above:

- For Research Question #1 and #2:

- ***FFK*** and ***NORDIHYDROGUAIARETIC ACID***: a total of 77 searches were performed.

- For Research Question #3 and #4:
  - ***NAK*** and ***BrCaK*** (2 searches): a total of 63 searches were performed.
- For Research Question #5 and #6:
  - ***FFK*** and ***NAK*** and ***BrCaK***: a total of 266 searches were performed.

- **STEP 2**: The next step was analysis of the documents. Each abstract was examined for biomedical and discipline specific connections to the study. Copies of the full document were obtained from interlibrary loans when further analysis was necessary. The full documents were analyzed for content matching the attributes of functional foods, NDGA and breast cancer as defined in this study. A total of 60 documents were examined and analyzed and 31 documents were included in the study for author cocitation analysis.
- **STEP 3**: The author cocitation analysis was conducted. The documents retrieved from the bibliographic searches on the seven databases conducted in Step 1 provided the documents and authors for analysis. Each document was analyzed to determine its relevancy to this study. Then the authors, as the unit of analysis, were entered into SciSearch® (SciSearch) an electronic science citation index database (® Institute for Scientific Information [ISI®] Thomson Scientific, Philadelphia, PA). The SciSearch files were downloaded for manipulation of the bibliographic data.

  BibExcel, a free-ware tool box for manipulating bibliographic information which was developed by Olle Persson, Inforsk, Umea University, Sweden http://www.umu.se/inforsk/Bibexcel was used to analyze the target literatures on

functional foods and NDGA and the source literature on breast cancer. Microsoft® Excel (Excel), a spreadsheet program (® Microsoft Corporation, Redmond, WA) was also used to organize and arrange the data from BibExcel. Due to the variable nature of the downloaded records, extensive editing, alignments and corrections were necessary prior to loading into BibExcel for the application of bibliographic analysis techniques. The downloaded file was converted to a text file, with exacting tag format achieved by the use of invisibles (spaces, paragraph marks), commas, single and double spikes. The prepared data was loaded into BibExcel and the following types of files were produced:

1. A cited reference (CR) file with author, date, volume and journal title was produced as an xxx .out file.
2. A frequency distribution file of cited authors, with duplicates removed, was produced as an xxx .oux file. From the xxx .oux file the author cocitation frequencies were calculated for each set of literatures.
3. A file with author name, journal name, year, country of publication, afflitation/organization, for each author was produced.

The above files were examined and author cocitation analysis counts were based on a list of authors *jointly cited* in a third document.

- **Step 4:** The final step was analyzing results. The results are reported in Chapter IV. The literatures on functional foods, NDGA and the literature on breast cancer prevention, were analyzed. These literatures are identified as complementary. In this context, a state of complementarity is defined as being logically, biologically and scientifically related in content and perspective.

The bibliometric technique of cocitation analysis was utilized to establish connectedness and interactivity, or conversely the condition of disjointness, between the sets of bioscientific literature. If two documents are simultaneously cited by a third document, they are co-cited, or have the characteristic of cocitation (Diodato, 1994). Cocitation is a means of establishing and reflecting a major link in perspective, study and research (Small, 1980; Swanson, 1987, 1991; McCain, 1991; Smalheiser & Swanson, 1994; Swanson & Smalheiser, 1996a, 1996b, 1997). Therefore, the absence of cocitation identifies the condition of disjointness and is a link to potentially undiscovered knowledge. The condition of disjointness means the literatures have no articles in common, do not cite or mention each other, and have minimal to no cocitations in common.

The condition of disjointness and the efficacy of cocitation analysis were further supported by an in-depth analysis of other variables that assisted in explicating the knowledge synthesis discovery. These variables included analysis of the primary document content focus, proximity in time of the citation and/or cocitation, and the year of publication of the documents.

In summary, the methodological steps of document retrieval and data analysis were as follows:

1. Conducted the database searches in six databases with the established parameters.
2. Obtained copies of documents identified by the bibliographic analysis.
3. Analyzed the documents for specified biomedical and/or nutritional connections.
4. Established disjointness via a search in SciSearch and BibExcel.
5. Assembled and correlated the data.

6. The documents were analyzed for journal tile, year of publication, country of publication and author affilitation.
7. The results of all analysis were correlated and recorded.

CHAPTER IV

RESULTS and ANALYSIS

This research began with combinatorial keyword searches that identified the authors who had published documents in the target literatures of functional foods and nordihydroguaiaretic acid (NDGA), and the source literature on breast cancer. The searches were conducted in publicly accessible databases, for dates January 1980 through May 2002.

The principle bibliographic technique used in this research was author cocitation analysis (ACA). The authors are the units of analysis and two sets of authors' names were retrieved via combinatorial keyword searching of the target and source literatures. Six databases were searched and the targeted documents retrieved. Many of the document retrievals were duplicated in several databases. The retrieved documents were analyzed for relatedness to the current research protocol. Authors of documents related to this research compose the author cocitation analysis (ACA) units.

The authors of the retrieved documents are the units of analysis. When the literature on functional foods and nordihydroguaiaretic acid was searched, there were 10 unique authors retrieved and included in the cocitation analysis. The search of nordihydroguaiaretic acid and breast cancer retrieved 21 unique authors for inclusion in the cocitation analysis. No new authors were retrieved for functional foods, nordihydroguaiaretic acid and breast cancer. Three of the authors from the literature sets were crossovers between the (1) functional foods and NDGA and (2) NDGA and breast cancer literatures. These crossover authors were Harper, A., Sathymoorthy, N. and Schultze-Mosgau, M. The authors for each sets of literatures used in the cocitation analysis, and their document citations are listed below:

Target literatures: Functional Foods and NDGA:

1. Blalock, J.E., Archer, D., & Johnson, H. (1981). Anticellular and immunosuppressive activities of foodborne phenolic compounds. *Proceedings of the Society for Experimental Biology and Medicine. 167(3), 391-393.*
2. Garreau, B., Vallette, G., Adlercreutz, H., Wahala, K., Makela, T., Benassayag, C., & Nunez, E. (1991). Phytoestrogens: New lignands for rat and human alpha-fetoprotein. *Biochimica et Biophysica Acta.* 1094(3), 339-345.
3. Harper, A., Kerr, D., Gescher, A. & Chipman, J. (1999). Antioxidant effects of isoflavonoids and lignans, and protection against DNA oxidation. *Free Radical Research.* 31(2), 149-160.
4. Martin, M.E., Haourigui, M, Pelissero, C., Bennassayag, C., & Nunez, E.A. (1996). Interactions between phytoestrogens and human sex steroid binding protein. *Life Science.* 58(5), 429-436.
5. Morikawa, M., Fukuchi, K., Inoue, E., & Tsuboi, M. (1992). Effect of mammalian lignans on fMLP-induced oxidative bursts in human polymorphonuclear leukocytes. *Journal of Pharmacy and Pharmacology.* 44(10), 859-861.
6. Park, S., Lee, D., & Yang, C. (1998). Inhibition of fos-jun-DNA complex formation by dihydroguaiaretic acid and in vitro cytotoxic effects on cancer cells. *Cancer Letters.* 127(1-2), 23-28.
7. Sathyamoorthy, N., Wang, T., & Phang, J. (1994). Stimulation of pS2 expression by diet-derived compounds. *Cancer Research.* 54(4), 957-962.
8. Schegg, K.M. & Welch, A. (1984). The effect of nordihydroguaiaretic acid and related lignans on formyltetrahydrofolate synthetase and carboxylesterase. *Biochimica et Biophysica Acta.* 788(2), 167-180.
9. Schottner, M. , Spiteller, G., & Gansser, D. (1998). Lignans interfering with 5 alpha-dihydrotestosterone binding to human sex hormone-binding globulin. *Journal of Natural Products.* 61(1), 119-121.
10. Schultze-Mosgau, M.H., Dale, I., Gant, T., Chipman, J., Kerr, D. & Gescher, A. (1998). Regulation of c-fos transcription by chemopreventive isoflavonoids and lignans in MDA-MB-468 breast cancer cells. *European Journal of Cancer.* 34(9), 1425-1431.

Source Literature: Breast Cancer

1. Ara, G. & Teicher, BA. (1996). Cyclooxygenase and lipoxygenase inhibitors in cancer therapy. *Prostaglandins, Leukotrienes and Essential Fatty Acids.* 54(1), 3-16.
2. Buckman, DK., Hubbard, N. & Erickson, K.(1991). Eicosanoids and linoleate-enriched growth of mouse mammary tumor cells. *Prostaglandins, Leukotrienes and Essential Fatty Acids.* 44(3), 177-184.
3. Cunningham, DC, Harrison, L. & Shultz, T. (1997). Proliferative responses of normal human mammary and MCF-7 breast cancer cells to linoleic acid, conjugated linoleic acid and eicosancid synthesis. *Anticancer Research.* 17(1A), 197-203.
4. Damtew, B & Spagnuolo, R. (1997). Tumor cell-endothelial cell interactions: Evidence for roles of lipoxygenase products of arachidonic acid in metastasis. *Prostaglandins, Leukotrienes and Essential Fatty Acids.* 56(4), 295-300.

5. Earashi, M, Noguchi, M & Tanaka, M. (1996). *In vitro* effects of eicosanoid synthesis inhibitors in the presence of linoleic acid on MDA-MB-231 human breast cancer cells. *Breast Cancer Research and Treatment.* 37(1), 29-37.
6. Earashi, M., Noguchi, M., Kinoshita, K. & Tanaka, M. (1995). Effects of eicosanoid synthesis inhibitors on the *in vitro* growth and prostaglandins E and leukotriene B secretion of a human breast cancer cell. *Oncology.* 52(2), 150-155.
7. Earachi, M, Endo, Y., Obata, T., Minami, M., Noguchi, M., Miyazaki, I. & Sasaki, T. (1996). Effects of linoleic acid and eicosanoid synthesis inhibitors on the growth and c-myco oncogene expression of human breast cancer cells. *International Journal of Oncology.* 8(1),145-151.
8. Fulton, AM., Lattera, J.& Hanchin, C. (1989). Prostaglandin E2 receptor heterogeneity and dysfunction in mammary tumor cells. *Journal of Cell Physiology.* 139(1), 93-97.
9. Harper, A., Kerr, D., Gescher, A. & Chipman, J. (1999). Antioxidant effects of isoflavonoids and lignans and protection against DNA oxidation. *Free Radical Research.*31 (2), 149-160.
10. Hofmanova, J., Musilova, E. & Kozubik, A. (1996). Suppression of human cancer cell proliferation by lipoxygenase inhibitors and gamma-radiation *in vitro*. *General Physiology and Biophysics.* 15(4), 317-431.
11. Hsiao, WL, Pal, H., Matsui, M. & Weinstein, I. (1990). Effects of specific fatty acids on cell transformation induced by an activated c-H-ras oncogene. *Oncogene.* 5(3), 417-421.
12. Johanning, GL. & Lin, T. (1995). Unsaturated fatty acid effects on human breast cancer cell adhesion. *Nutrition and Cancer.* 24(10), 57-66.
13. Kim, RS, Zaaborniak, C., Begleiter, A. & LaBelle, F. (1992). Antiproliferative properties of aminosteroid antioxidants on cultured cancer cells. *Cancer Letters.* 64(1), 61-66.
14. Noguchi, M., Rose, DP, Earashi, M. & Miyazaki, I. (1995). The role of fatty acids and eicosanoid synthesis inhibitors in breast carcinoma. *Oncology.* 42(4), 265-271.
15. Lambert, JD, Meyers, R., Timmerman, B., & Dorr, R. (2001). tetra-O-methylnordihydroguaiaretic acid inhibits melanoma *in vivo. Cancer Letters.* 171(1), 47-56.
16. Palmantier, R., Roberts, J., Glasgow, W., Eling, T. & Olden, K. (1996). Regulation of the adhesion of a human breast carcinoma cell line to type IV collagen and vitronectin: Roles for lipoxygenase and protein kinase. *Cancer Research.* 56(9), 2206-2212.
17. Reddy, N, Everhart, A., Eling, T. & Glasgow, W. (1997) Characterization of a 15-lipoxygenase in human breast carcinoma BT-20 cells: Stimulation of 13-HODE formation by TGF alpha/EGF. *Biochemical Biophysical Research Communications.* 231(1), 111-116.
18. Rose, DP. & Connolly, J. (1990). Effects of fatty acids and inhibitors of eicosanoid synthesis on the growth of a human breast cancer cell line in culture. *Cancer Research.* 5(922), 7139-7144.
19. Sangeetha, Sagar P., Das, UN., Koratkar, R., Ramesch, G., Padma, M. & Sravan, K. (1992). Cytoxic action of cis-unsaturated fatty acids on human cervical carcinoma (HeLa) cells: Relationship to free radicals and lipid peroxidation. *Cancer Letters.* 63(3), 189-198.
20. Sathyamoorthy, N., Wang, T. & Phang, J. (1994). Stimulation of pS2 expression by diet derived compounds. *Cancer Research.* 54(4), 957-61.

21. Schultze-Mosgau, MH, Dale, I., Gant, T., Chipman, J., Kerr, D. & Gescher, A. (1998). Regulation of c-fos transcription by chemopreventive vs. isoflavonoids and lignans in MDA-MB-468 breast cancer cells. *European Journal of Cancer.* 34(9), 1425-1431.

Annotated bibliographies of the sets of literature are in Appendix F and Appendix G.

Functional Foods and NDGA

The first combinatorial keyword searches were conducted on selected functional foods synonym terms and related terms in combination with nordihydroguaiaretic acid (NDGA). The search began for connections between functional foods and NDGA. NDGA was discussed as a lignan in seven databases, with duplication of articles in all databases, i.e., retrieval of the same document from the each database. NDGA was linked with the food additive term in two of the databases. Table M lists the combinatorial keyword search, the database, and the number of documents retrieved per database.

FUNCTIONAL FOODS & NDGA: Synonym-like terms	**DATABASES**						
	Pub Med[a]	**BIOSIS**	**EMBASE**	**CANCERLIT**	**CAB Health**	**Food Sci/Tech**	**IBIDS**
1. Additives, food	1[1]	0	0	1	0	0	0
2. Cosmeceuticals	0	0	0	0	0	0	0
3. Designer foods	0	0	0	0	0	0	0
4. Genetic foods	0	0	0	0	0	0	0
5. Genetically-engineered Foods	0	0	0	0	0	0	0
6. Medicinal foods	0	0	0	0	0	0	0
7. Nutraceuticals	0	0	0	0	0	0	0
8. Pharmafoods	0	0	0	0	0	0	0
9. Therapeutic foods	0	0	0	0	0	0	0
10.Lignans	16[13]	5	12 [4]	5	3 [3]	1	8
11 Prebiotics	0	0	0	0	0	0	0
TOTAL DOCUMENTS RETRIEVED: 52 **NUMBER OF UNIQUE DOCUMENTS RETRIEVED: 21**							

Note: [a] The first unique documents are numbered in the PubMed column.

Table M: Functional Foods and NDGA Documents Retrieved

A total of 52 documents were retrieved, of which 21 were unique, non-repeated documents. Nine of the documents on lignans and the one document on food additives were included in the cocitation analysis. The criteria for inclusion in the analysis were as follows:

1. Identification or discussion of NDGA as a functional food;
2. Identification or discussion of NDGA as a preventative for cancer;
3. Discussion of lignans as preventative for cancer;
4. Discussion of characteristics of NDGA shared with functional foods in general;
5. Discussion of properties of functional foods chemopreventative attributes which are known attributes of NDGA.

Eleven of the documents on lignans that were retrieved with functional foods and NDGA were not included in the analysis because they did not meet criteria for inclusion. The 11 documents were excluded for the following reasons:

1. NDGA as a treatment for a hematophagous bug (Rhodnius prolixus) was discussed in two of the documents.
2. NDGA as a treatment for human immunosuppressive virus (HIV) or human papilloma virus was discussed in five of the documents.
3. The role of NDGA in inflammation caused by an antimycotic agent was discussed in one document.
4. Synthesis of NDGA or tests for antioxidant properties of NDGA was discussed in two documents.
5. NDGA and another lignan were compared in one document.

The search with the synonym ‘food additive’ and NDGA retrieved the same document from two databases. This document by Blalock (1981) specifically addresses NDGA as a phenolic foodborne substance, and phenolic compounds are known cancer chemopreventative agents.

The 10 authors that met the criteria were entered into SciSearch and the results are presented in Table N. Table N lists authors, total number of citations per author, cocitation frequencies and the specific authors cocited.

	AUTHORS NAMES	TOTAL NUMBER CITATIONS	COCITATION FREQUENCY	SPECIFIC COCITATIONS
a.	**Blalock, J E**	10	0	
b.	**Garreau, B**	27	15	d (10), g (4), h (1)
c.	**Harper, A**	7	0	
d.	**Martin, M E**	38	20	b (9), g (9), i (2)
e.	**Morikawa, M**	2	0	
f.	**Park, S**	16	0	
g.	**Sathyamoorthy, N**	58	14	b (4), d (7), i (2), j (1)
h.	**Schegg, K M**	8	0	
i.	**Schottner, M**	2	0	
j.	**Schultze-Mosgau, M H**	6	2	g (1), i (1)

Note. The specific numbers of cocitations are enclosed in parenthesis in column five.

Table N: Functional Foods and NDGA Author Cocitations

Research question #1: "Will cocitation analysis of the public literature on functional foods and nordihydroguaiaretic acid, exclusive of the breast cancer literature, reveal undiscovered connections?" is answered in the affirmative. The synonyms for functional foods retrieved one document on the keyterm 'food additive', authored by Blalock (1981) and no cocitations were made. A minimal or absent cocitation in complimentary literatures constitutes an undiscovered connection (Swanson, 1987). However, there are connections between functional foods and the specific *attributes* of NDGA. A summary analysis demonstrates the following:

1. Ten authors were retrieved via combinatorial keyword searches.
2. There were 51 cocitations for four authors; six authors were without cocitations.
3. One author was retrieved from the 'food additive' term and had no cocitations.
4. Nine authors were retrieved with NDGA as a 'lignan', with 164 citations and 51 cocitations.
5. Nine combinatorial keyword searches did not retrieve any authors from keyword searches.

The functional food literature specifically discusses NDGA as a food additive in one document, and incorporates by default NDGA as a lignan in nine documents. The remaining nine combinatorial keyword searches did not uncover an author/document connection between functional foods and NDGA. Nine of the 10 documents report research conducted on NDGA as a lignan and describe the examined attribute, i.e., the connection to functional foods is through the designation of NDGA as a lignan. The document by Blalock (1981) describes NDGA as a foodborne phenolic compound or food additive. Author cocitation analysis (ACA) on Blalock showed 10 total citations and no cocitiations, thus being the only authored document meeting the criteria for minimum cocitations for undiscovered connections. Five of the remaining nine authors had no cocitations.

Research question #2: "Will cocitation analysis of the public literature on functional foods and nordihydroguaiaretic acid, exclusive of the breast cancer literature, reveal linkages of a possible preventative agent?" is answered in the affirmative. There were 10 documents with statements showing linkages of functional foods and NDGA as a possible preventative agent, with 51 cocitations. The 10 authors are listed in Table N and included in the cocitation analysis.

An annotated bibliography of the ten authors retrieved with combinatorial keyword searching of functional foods and NDGA is available in Appendix G. The annotation explicitly states attributes of NDGA that are possibly chemopreventative. In summary, these attributes are: (1) NDGA is a phenolic compound with immunosuppressive properties; (2) NDGA is a lignan, with antioxidative properties; (3) NDGA inhibits certain enzyme systems which may be significant in disrupting cellular energy, such as in cancerous growths; (4) NDGA interferes with mitogenic signal conduction between cells; (5) NDGA inhibits certain hormone binding, which

may have implications for hormone dependent tumors, and (6) NDGA suppresses tumor activity *in vitro.* These are functions examined widely in the functional foods research front.

Functional food documents only minimally address NDGA even though the linkage is apparent on independent examination. The near lack of obvious linkage is consistent with the absence to limited use of NDGA in the food industry in the United States since 1968. The connections between functional foods and NDGA support Hypothesis $_1$:

> In the syllogistic paradigm of A intersection B, a literature search of the human and animal cell research with nordihydroguaiaretic acid will establish characteristics of nordihydroguaiaretic acid shared with functional foods.

Functional foods that have been extensively researched as preventative agents are frequently classified as (1) antioxidants, (2) prebiotics, and (3) lignans. NDGA is a prototype antioxidant, a lignan and could function as a prebiotic lignan. Connections and linkages to these latter attributes of NDGA as a functional food are indirect and require exposition to demonstrate the linkages. NDGA is a known antioxidant and many functional foods have antioxidant properties. The attribute of NDGA, singularly, as a prototype antioxidant, was subtracted from the functional foods retrieval list because NDGA is well established as an antioxidant. A search on PubMed listed 1174 documents on NDGA and antioxidants, from1980 to May 2002. Thus, while antioxidant properties indeed effect cancer manifestations, it is a cumulative property of NDGA rather than a newly discovered attribute.

NDGA is a lignan naturally produced in a non-food plant. However, NDGA shares biochemical characteristics with other lignans, such as oilseeds, (e.g., flaxseed) whole grains, vegetables and fruits (Niemeyer & Metzler, 2001). This attribute is a linkage between functional foods and NDGA as a possible preventative for breast cancer. In the human intestinal tract lignans are acted upon by bacterial flora and ultimately separated into component parts of

estrogen-like biochemicals that are considered chemopreventative for breast cancer (Aldercruetz, 2002; Aldercruetz, 2001; Niemeyer & Metzler, 2001; Croteau, Kutchan, & Lewis, 2000; Pool-Zobel, 2000; Meagher, 2000; Steinmetz & Potter, Sept, 1991 and Nov. 1991; Kohlmeier & Mendez, 1970).

NDGA and Breast Cancer:

Research question #3: "Will cocitation analysis of the public literature on nordihydro-guaiaretic acid and the public literature on breast cancer, reveal undiscovered connections?" is answered in the negative, as the connection between nordihydroguaiaretic acid and breast cancer is not an undiscovered connection. The database retrievals of documents on nordihydroguaiaretic acid and breast cancer / breast neoplasm are listed in Table O below.

NDGA & BREAST CANCER: Search Terms	**DATABASES**						
	PubMed[a]	**BIOSIS**	**EMBASE**	**CANCERLIT**	**CAB Health**	**Food Sci/Tech**	**IBIDS**
1. NDGA & breast cancer	11[11]	1	9 [5]	11	0	0	11 [2]
2. NDGA & breast							
neoplasm	0	0	0	10 [0]	0	0	0
TOTAL NUMBER DOCUMENTS RETRIEVED: 53 NUMBER OF UNIQUE DOCUMENTS RETRIEVED: 18							

Note. [a] The numbers of unique documents are first listed in the PubMed column.

Table O: NDGA and Breast Cancer/Neoplasm
Documents Retrieved

A total of 53 documents on NDGA and breast cancer/breast neoplasm yielded 18 unique, non-repeated documents. These 18 unique documents were included in the author cocitation analysis. The 18 documents retrieved that are specifically related to breast cancer/neoplasm, demonstrate the connections between NDGA and breast cancer. The documents demonstrated a persistent research front on NDGA as a potential chemopreventative agent, as well as addressing the continuing connection between nutrition, food and breast cancer. As anticipated, documents retrieved from PubMed and CANCERLIT databases were quite similar in the number of

documents retrieved for the terms 'NDGA and breast cancer', with 11 documents each. One of the documents from CANCERLIT was not included in the ACA. This document was an abstract on a conference meeting, and the same author and document was published in a journal that was included in the ACA analysis. NDGA and breast neoplasm as combined terms were retrieved only from CANCERLIT, as breast cancer is the more commonly used term. The IBIDS database reported 11 documents, which was predictable as this database focuses on botanical preparations. A summary analysis of the 18 unique documents follows:

1. NDGA was researched as a lipoxygenase inhibitor for a breast cancer cell line in nine documents.
2. NDGA was researched as an eicosanoid synthesis inhibitor for a breast cancer cell line in two documents.
3. NDGA was researched as a chemical that produces apoptosis in breast cancer cells in one document.
4. NDGA was researched and reported as eliciting an estrogen-like response in relation to breast cancer, in one document.
5. NDGA was reported as interfering with signal transduction and breast cancer cells in one document.
6. NDGA was reported to reduce breast cancer cell adhesion in one document.
7. NDGA's effect on breast cancer in its capacity as an antioxidant was reported in three documents.

An annotated bibliography on NDGA and breast cancer prevention is in Appendix H. NDGA has been researched extensively for its biochemical action on tissues in the laboratory setting, e.g., *in vitro*, and this research was conducted to demonstrate any possible connection to *in vivo* research on human beings.

Research question #4: " Will cocitation analysis of the public literature on nordihydro-guaiaretic acid and the public literature on breast cancer, reveal linkages of a possible preventative agent?" is answered in the affirmative. A combinatorial search was conducted for nordihdyroguaiaretic acid and breast cancer and scientific terms related to chemoprevention. The scientific search terms depicted a biochemical or oncological property of a chemopreventative

agent such as NDGA, plus several terms logically related to a chemical used for medicinal purposes. These searches retrieved 10 documents and 3 distinct documents with NDGA as an antioxidant and related to breast cancer. No human *in vivo* document connections were retrieved. Table P lists the terms, databases and number of documents retrieved for NDGA and breast cancer.

NDGA & BREAST CANCER: Search terms	**DATABASES**						
	PubMed	**BIOSIS**	**EMBASE**	**CANCERLIT**	**CAB HEALTH**	**Foodline**	**IBIDS**
1. Anticarcinogen	0	0	0	0	0	0	0
2. Antioxidant	9 (3)	0	1	0	0	0	0
3. Antimutagen	0	0	0	0	0	0	0
4. Antitumorigenic	0	0	0	0	0	0	0
5. Chemopreventative agent	0	0	0	0	0	0	0
6. Chemopreventive agent	0	0	0	0	0	0	0
7. Phytopharmacognacy	0	0	0	0	0	0	0
8. *in vivo*	0	0	0	0	0	0	0
TOTAL DOCUMENTS RETRIEVED: 10 **NUMBER OF UNIQUE DOCUMENTS RETRIEVED: 3 ***							

Note. * The numbers of unique documents are identified in parenthesis in each column,

Table P: NDGA Terms and Breast Cancer/ Neoplasm
Documents Retrieved

Nordihydroguaiaretic acid and breast cancer and antioxidant documents were retrieved with combinatorial keyword searches 10 times and only 3 documents were unique for this group of retrievals. The seven documents had previously been retrieved with only the two-keywords nordihydroguaiaretic acid and breast cancer. NDGA is a well-known antioxidant and has been extensively researched as an antioxidant in other relationships. All of the 10 authors are included in the ACA, i.e., Cunningham, Earachi , Johanning, Kim, Noguchi, Reddy, Rose, Sangeetha, Sathyamoorthy, and Schultze-Mosgau. The other six keyword terms did not retrieve articles with all three keywords. Author cocitation analysis revealed cellular *in vitro* research and explanatory documents linking breast cancer prevention and NDGA. There is considerable cocitation

activity, demonstrating connectedness and interactivity between the two sets of literature. The author cocitation analysis for NDGA and breast cancer is in Table Q:

	AUTHOR Names	TOTAL Number of Citations	COCITATION Frequency	SPECIFIC Cocitations
a.	Ara, G	16	4	h (1), o (1), r (2)
b.	Buckman, D K	7	45	h (2), l (1), o (2), q (1), r (39)
c.	Cunningham, D C	14	2	h (1), o (1)
d.	Damtew, B	1	4	e (1), r (2), s (1)
e.	Earashi, M	16	39	b (2), c (2), d (1), h (5), l (1),o(3), q (1), r (22), s (2)
f.	Earashi, M	3	21	h (1), o (3), r (17)
g.	Earashi, M	2	0	
h.	Fulton, A M	20	5	b (1), o (2), r (2)
i.	Harper, A	7	0	
j.	Hofmanova, J	6	3	o (2), r (1)
k.	Hsiao, W L	12	0	
l.	Johanning, G L	14	47	b (1), f (3), h (2), o (4), p (3), q (2), r (32)
m.	Kim, R S	11	0	
n.	Lambert, JD	1	0	
o.	Noguchi, M	1	1	r (1)
p.	Palmantier, R.	7	2	l (1), r (1)
q	Reddy, N	14	54	a (2), b (21), e (3), h(2), l (3),o (5), r (18)
r.	Rose, D P	18	11	a (1), b (3), d (1), h (1), l (1), o (4)
s.	Sangeetha, Sagar P	2	0	
t.	Sathyamoorthy, N	58	16	r (15), u (1)
u.	Schultze-Mosgau, M H	6	1	t (1)

NOTE. The numbers of cocitations are enclosed in parenthesis in column five.

Table Q: NDGA and Breast Cancer Author Cocitations

Author cocitation analysis disclosed a connection and linkage between NDGA and breast cancer as conducted by cellular *in vitro* research in 14 out of 21 cociting authors. These 21 authors have been consistently present in sets of documents retrieved in this study. The reported *in vitro*

research has been conducted on cultured human breast cell lines and laboratory mammals, such as rats and mice.

Functional Foods, NDGA and Breast Cancer/Neoplasm,

Research question #5: "Will cocitation analysis of the public literature on functional foods, nordihydroguaiaretic acid and the public literature on breast cancer, reveal undiscovered connections?" is answered in the negative. There are known connection between functional foods, NDGA and breast cancer. Author cocitation analysis demonstrates connections and linkages for *in vitro* research. In addition, specific definitive linkages between functional foods, NDGA, and breast cancer/neoplasm are ascribed to the document retrievals that are 'crossovers', i.e., retrieved in two different literature set searches. The 'crossover' documents and authors were retrieved from both the search on functional foods and NDGA and the search on NDGA with breast cancer/neoplasm. The three 'crossover'researchers are working with NDGA in the functional foods area, and are also working in the NDGA and breast cancer area. The author cocitations for Sathyamoorthy had 15 cocitations for functional foods and NDGA and 18 cocitations on NDGA and breast cancer. Author Schultze-Mosgau had two cocitations for functional foods and NDGA and one for NDGA and breast cancer. Table R lists the 'crossover' authors, cocitation frequency and number of documents retrieved for both sets of literature.

'Crossover'Authors	**Functional Foods & NDGA**		**NDGA & Breast Cancer/Neoplasm**	
	Cocitation Frequency	**Number of Retrievals**	**Cocitation Frequency**	**Number of Retrievals**
1. Harper, A.	0	7	0	7
2. Sathyamoorthy, N.	15	58	18	58
3. Schultze-Mosgau, M.	2	6	1	6

Table R: 'Crossover' Documents Retrieved for Functional Foods & NDGA and NDGA & Breast Cancer

A separate analysis of two terms related to breast cancer and NDGA warrant exposition. The contribution of oxidative stress to the development of breast cancer in humans has been studied and explored fairly extensively. In a listing retrieved exclusively with breast cancer and antioxidants, 28 documents were retrieved from BIOSIS Previews, delineating the following three aspects:

1. Antioxidants are chemopreventative for breast cancer.
2. Antioxidants are chemopreventative for hormonal-induced carcinogenesis.
3. Diet and nutritional intake is highly associated with breast cancer and breast cancer prevention, particularly the ingestion of phenolic compounds.

The obvious connection is: NDGA is a potent phenolic antioxidant and can be a food source. However, NDGA was not included in the research reported in 28 documents on breast cancer and antioxidants.

The second item for exposition relates to NDGA as an antimutagenic agent. Three documents retrieved reported NDGA as an antimutagen, and 13 documents retrieved were related to breast cancer and antimutagenic agents exclusively. The three documents on NDGA discussed its properties of being a phenolic lignan with *in vitro* and *in vivo* antimutagenic attributes, but did not include any references to breast cancer. The 13 documents on breast cancer and antimutagens focused primarily on contraceptive drugs and did not include NDGA as an antimutagenic agent.

Research question #6: "Will cocitation analysis of the public literature on functional foods, nordihydroguaiaretic acid and the public literature on breast cancer, reveal linkages of a possible preventative agent?" is answered in the affirmative. In the final combinatorial keyword search, the terms were functional foods synonyms, NDGA scientific function terms, and breast cancer/breast neoplasm. Searching with the three, keyword combinations did not retrieve any

food additive documents and only 12 lignan related documents, 5 of which were unique. Two documents were not included in the ACA as they related NDGA to HIV suppression or its use as an insecticide. The three remaining unique documents (Harper, Sathyamoorthy and Schultze-Mosgau) were previously retrieved with only the two terms NDGA and breast cancer, and were included in the ACA. Ten documents with antioxidant terminology were retrieved, with three unique documents. All 10 of the documents and authors were previously retrieved and are included in the ACA. No human *in vivo* documents were retrieved. The search terms, databases with number of retrievals, and the number of unique retrievals are displayed in Table S.

FUNCTIONAL FOODSs NDGA, BREAST CANCER/NEOPLASM, SYNONYMS, & FUNCTION: SEARCH TERMS	**DATABASES**						
	PubMed	**BioSIS**	**EMBASE**	**CANCERLIT**	**Cab Health**	**Foodline**	**IBIDS**
1. Additives, food	0	0	0	0	0	0	0
2. Cosmeceuticals	0	0	0	0	0	0	0
3. Designer foods	0	0	0	0	0	0	0
4. Genetic foods	0	0	0	0	0	0	0
5. Genetically-engineered foods	0	0	0	0	0	0	0
6. Lignans	2 (2)	5 (2)	2	2	1(1)	0	0
7. Medicinal foods	0	0	0	0	0	0	0
8. Nutraceuticals	0	0	0	0	0	0	0
9. Pharmafoods	0	0	0	0	0	0	0
10. Therapeutic foods	0	0	0	0	0	0	0
11. Prebiotics	0	0	0	0	0	0	0
12. Anticarcinogen	0	0	0	0	0	0	0
13. Antioxidant	9 (3)	0	1	0	0	0	0
14. Antimutagen	0	0	0	0	0	0	0
15. Antitumorigenic	0	0	0	0	0	0	0
16. Chemopreventative	0	0	0	0	0	0	0
17. Chemopreventive	0	0	0	0	0	0	0
18. Phytopharmacognacy	0	0	0	0	0	0	0
19. *in vivo*	0	0	0	0	0	0	0
TOTAL DOCUMENTS RETRIEVED: 22 **NUMBER OF UNIQUE DOCUMENTS RETRIEVED: 8**							

Note: The numbers of unique documents in the database are identified in parenthesis following the number of documents retrieved.

Table S: Functional Food, NDGA, Breast Cancer/ Neoplasm, Synonyms & Scientific Terms

Twenty-two documents were retrieved with the search terms for functional foods, NDGA and breast cancer prevention. Eight of the documents were unique, non-repeated documents in the databases. Analysis of the functional foods, NDGA and breast cancer documents provide support for connectiveness between the sets of literature, but primarily the analysis demonstrates the lack of human *in vivo* research on breast cancer and NDGA as a chemopreventative, functional food agent. The retrieved documents demonstrate properties of NDGA functional against breast cancer *in vitro* only.

Implicit connections between functional foods, NDGA and breast cancer have been identified in this study. The literature review and the search interpretations provide evidence of these connections. Table T collates these implicit but indirect connections and provides arguments to support the connections.

Implicitly connected arguments for functional foods and NDGA as chemopreventive for breast cancer.	
Functional foods and NDGA	Breast Cancer
1. Many functional foods are plant secondary metabolites, and may be lignans and/or antioxidants.	1. Dietary intake is considered to a causal factor in 35% to 50% of cancers, inclusive of breast cancer (Williams & Wynder, 1996).
2. NDGA is a secondary metabolite of the *Larrea tridentata* plant, and is both a lignan and antioxidant.	2. Non-food substances which are chemopreventive may be added to plants or ingested as food or taken as pharmaceuticals.
3. Lignans are metabolized by intestinal microflora. Lignans may be ingested a part of a plant or synthesized by intestinal bacteria, then they undergo enterohepatic circulation and are returned to the intestine.	3. The mammalian phytoestrogens enterodiol and enterolactone are produced in the colon by the action of bacteria on the plant precursors matairesinol (MAT), secoisolariciresinol (SECO), and other precursors in the diet. Both MAT and SECO have been shown to possess estrogenic and antiestrogenic activities.

Implicitly connected arguments for functional foods and NDGA as chemopreventive for breast cancer.	
4. NDGA and other functional foods have estrogenic and antiestrogenic attributes.	4. Antiestrogenic activity of MAT and SECO have been shown to protect against breast cancer.
5. Plant secondary metabolites are currently a research focus in nutritional science and biopharmacology.	5. Chemoprevention of breast cancer is preferred over treatment for the disease.

Table T: Indirect Connections Supportive of NDGA as Chemopreventive for Breast Cancer

In order to provide support and further substantiate the attributes of NDGA that are potentially chemopreventative, a search was conducted on terms directly related to NDGA and laboratory research on cancer cells. Specific research conducted on breast cancer cell lines and NDGA was included in order to demonstrate the existing research front. The searches on 'breast cell line', 'cell line' and 'cell lines' were conducted to strengthen the connections and illustrate the *in vitro* connections with NDGA and breast cancer. All the documents retrieved were laboratory, *in vitro*, tissue culture-type research reports. These documents are not part of the primary analysis via ACA. They were included for additional information only. The search terms, databases searched and numbers of document retrieved are listed in Table U.

SEARCH TERMS	**DATABASES**						
	PubMed	**BIOSIS**	**EMBASE**	**CANCERLIT**	**CabHealth**	**Food Sci/Tech**	**IBIDS**
1. NDGA & breast cell line	14	0	2	2	0	0	7
2. NDGA & cell lines	39	9	3	0	0	0	8
3. NDGA & *in vivo*	133	19	136	19	0	0	65
4. NDGA & cell line	162	55	18	38	0	0	116

Table U: Additional Search Terms on NDGA and Cancer Research

Twenty-five documents on NDGA and breast cell line were retrieved, 15 of which were unique, non-repeats. Additionally 12 of these were also the same documents included in the NDGA and breast cancer search and were subjected to ACA. Fifty-nine documents were retrieved for NDGA and cell lines (plural), 46 of which were unique. The documents retrieved from NDGA and cell lines (plural) had 12 documents related to breast cancer cell lines, and 10 documents were in the NDGA and breast cancer retrievals. The other 47 documents reported research on cell types such as lung cancer cells, hemopoietic cells, murine lymphocytes, pancreatic cells, lymphoid cells, glioma spheres, prostate cell, melanoma cells, and cellular functions tested such as apoptosis, tumor cell respiration, cytolysis, and lipoxygenase inhibition.

NDGA and the term *in vivo* were searched to demonstrate the ongoing focus on NDGA with other mammals. A total of 372 documents were retrieved, the majority of which were distinct. However a search of the two terms, NDGA and *in vivo,* from PubMed retrieved a mixture of *in vivo* and *in vitro* research, predominately *in vitro*, i.e., 89 of 133 documents retrieved. This is apparently a consequence of the search engine programming. Not withstanding these phenomena, a number of explanatory documents were retrieved when searching for NDGA and the term *in vivo*. The titles of nine documents follow; the titles are explanatory of the content.

1. Ansar, S, Iqbal, M., Athar, M (1999): Nordihydroguaiaretic acid is a potent inhibitor of ferric-nitrilotriacetate-mediated hepatic and renal toxicity, and renal tumour promotion, in mice.

2. Diaz Barriga, S., Madrigal-Bujaidar, E., Marquez, P. (1999): Inhibitory effect of nordihydroguaiaretic acid on the frequency of micronuclei induced by methyl methanesulfonate *in vivo*.

3. Lambert, JD., Meyers, RO., Timmerman, BN., Dorr, RT. (2001): tetra-O-methyl-Nordihydroguaiaretic acid inhibits melanoma *in vivo.*

4. Madrigal-Bujaidar, E., Diaz Barriga, S., Cassani, M., Marquez, P., Revuelta, P. (1998): In vivo and in vitro antigenotoxic effect of nordihydroguaiaretic acid against SCEs induced by methyl methanesulfonate.

5. Ono, K., Hasegawa, K., Yoshiike, Y., Takashima, A., Yamada, M., Naiki, H. (2002): Nordihydroguaiaretic acid potently breaks down pre-formed Alzheimer's beta-amyloid fibrils *in vitro*.

6. Seufferlein, T., Seckl, MJ., Schwarz, E., Beil, M., Wichert, G., Baust, H., Luhrs, H., Schmid, R., Adler, G. (2002): Mechanisms of nordihydroguaiaretic acid-induced growth inhibition and apoptosis in human cancer cells.

7. Tang, DG. & Honn, Kv. (1997). Apoptosis of W256 carcinosarcoma cells of the monocytoid origin induced by NDGA involves lipid peroxidation and depletion of GSH: Role of 12-lipoxygenase in regulating tumor cell survival.

8. Ding, X., Kuszynski, C., El-Metwally, T. & Adrian, T. (1999). Lipoxygenase inhibition induced apoptosis, morphological changes and carbonic anhydrase expression in human pancreatic cancer cells.

9. Wang, Z., Agarwal, R., Zhou, Z., Bickers, D. & Mukhtar, H. (1991). Antimutagenic and antitumorigenic activities of nordihydroguaiaretic acid.

Three hundred eighty-nine documents were retrieved with NDGA and cell line (singular). Eight of the documents and authors (Earachi [twice], Hofmanova, Palmantier, Reddy, Rose, Johanning and Damtew) were duplicates from NDGA and breast cancer searches and were included in the ACA. The other documents reported research on murine cells, mouse and rat cells, hamsters, and various human cells, i.e., oral, tracheal, hematopoietic cells, glioma spheres and fibroblasts.

NDGA has been extensively researched and studied in various kinds of mammalian cancer cells. However, there were no human *in vivo* documents retrieved linking nordihydroguaiaretic acid and breast cancer. Therefore the research supports Hypothesis $_2$:

> In the syllogistic paradigm of B intersection C cocitation analysis of the breast cancer literature and nordihydroguaiaretic acid in *vivo* research will reveal an absence of linkages, therefore disjointness of the literatures.

Considerable research has been conducted on NDGA and breast cancer. All publicly accessible documents connecting human breast cancer prevention and NDGA were conducted *in vitro* on

human cells. There is an absence of human *in vivo* research on breast cancer with NDGA even though positive laboratory data is available.

Combinatorial keyword searches of the target and source literatures did not reveal any documents linking functional foods, NDGA and breast cancer via *in vivo* research techniques. This finding supports the absence of linkage between *in vivo* research for breast cancer and nordihydroguaiaretic acid as a functional food.

The establishment of NDGA as a chemopreventative functional food and the absence of *in vivo* research for breast cancer and NDGA as a functional food, supports hypothesis $_3$:

> In the syllogistic paradigm of A intersection B intersection C, an undiscovered public knowledge phenomena will be explicated, i.e., nordihydroguaiaretic acid is chemopreventative for breast cancer.

This undiscovered public knowledge phenomenon can be postulated as the beginning step for *in vivo* research demonstrating the chemopreventative properties of the lignan nordihydroguaiaretic acid. The logical next step would be marketing NDGA as a functional food, widely available to all women.

Analysis of Author Profiles

Continued analysis of the documents was conducted in order to support and strengthen the relationships between citing authors and the author cocitation analysis. Further examination of the author profiles was conducted. A file of the authors, journal titles, year of document publication, country of publication and affiliation/organization was compiled for the target literature authors and the source literature authors. Analysis of the file for NDGA and functional foods shows that 10 journals were represented, 5 countries of publication were represented, and 9 different affiliations or organizations in 8 countries were identified. The file is listed in Table V.

#	Author	Journal	Year	Country of Publication	Affiliation/Organization/ Corporate Source
1	Blalock, J E	Proceeedings of Society	1981	USA	U.S. government
		for Experimental Biology			
		and Medicine Society			
2	Garreau, B	Biochimica et Biophysics Acta	1991	Netherlands	INSERM, Faculte de Medecine
					Xavier Bichat, Paris, France
3	Harper, A	Free Radical Research	1999	United	School of Biochemistry,
				Kingdom	Univ. of Birmingham, U.K.
4	Martin, M E	Life Science	1996	France	INSERM, Faculte de Medecine
					Xavier Bichat, Paris, France
5	Morikawa, M	Journal of Pharmacy and	1992	United	Department of Pharmacology
		Pharmacology		Kingdom	Tokyo College of Pharmacy,
					Tokyo, Japan
6	Park, S	Cancer Letters (Ireland)	1998	Ireland	Department of Chemistry,
					Seoul National University,
					South Korea
7	Sathyamoorthy, N	Cancer Research	1994	USA	Laboratory of Nutritional and
					Molecular Regulation,
					National Cancer Institute,
					NIH, Maryland
8	Schegg, K M	Biochim et Biophysic Acta	1984	Netherlands	Department of Biochemistry
					University of Nevada, Reno, NV
9	Schottner, M	Journal of Natural Products	1998	USA	Lehrstuhl fur organisheChemie,
					Universitat Bayreuth,
					Germany
10	Schultze-Mosgau, M H	European Journal of Cancer	1998	England	MRC Toxicology Unit, University
					of Leicester, U.K.

Table V: Functional Foods and NDGA Author Profiles

The journals represented a wide range of disciplines, including neuroimmunology, oncology, biology, pharmacology, biochemistry, biophysics and natural products. The countries of publication represent Europe and the United States. In combination, the two author profiles indicate a very broad spectrum of interest in NDGA and functional foods. Interestingly, the affiliation support ranged from governmental to private schools of medicine, with the institutes represented inclusive of nutrititional molecular research facilities.

Similarly compelling information was discovered in examining the NDGA and breast cancer/neoplasm author profiles. The 21 authors were published in 14 different journals, published in 7 different countries, with 17 separate affiliations in 6 countries. These profiles

demonstrated global research and publishing interests related to NDGA and breast cancer. Fourteen of the authors published in 8 cancer-related research journals. Eight journals were published in the United Kingdom and seven journals were published in the United States. Table W lists the authors, journal of publication, year, country of publication and affiliation.

	Author	**Journal**	**Year**	**Country of Publication**	**Affiliation/Organization/ Corporate Source**
1.	Ara, G	Prostaglandins Leukotrienes and Essential Fatty Acids	1996	United Kingdom	Division of Cancer, Dana Farger Cancer Institute, MA, USA
2.	Buckman, D K	Prostaglandins Leukotrienes and Essential Fatty Acids	1991	United Kingdom	Hoffman-LaRoche Inc., Nutley, NJ
3.	Cunningham, D	Anticancer Research Essential Fatty Acids	1997	Greece	Department of Food Science and Human Nutrition, Washington State University
4.	Damtew, B	Prostanglandins Leukotrienes and Essential Fatty Acids	1991	United Kingdom	Department of Medicine, Case Western Reserve, Univ. School of Medicine at MetroHealth Medical Center, Cleveland, Ohio
5.	Earashi, M	Breast Cancer Research and Treatment	1996	Netherlands	Department of Surgery, Kanazawa Univ. Hospital, Japan
6.	Earashi, M	Oncology	1995	Switzerland	Department of Surgery, Kanazawa Univ. Hospital, School of Medicine, Japan
7.	Earashi, M	International Journal Of Oncology	1996	Greece	Department of Surgery, Toyama Central Hospital, Toyama, Japan
8.	Fulton, A M	Journal of Cell Physiology	1989	USA	E. Walter Albachten Department of Immunology, Michigan Cancer Foundation, Detroit
9.	Harper, A	Free Radical Research	1999	United Kingdom	School of Biochemistry Univ. of Birmingham, U.K.
10.	Hofmanova, J	General Physiology and Biophysiology	1996	Slovakia	Institute of Biophysics, Academy of Sciences of the Czech Republic

	Author	Journal	Year	Country of Publication	Affiliation/Organization/ Corporate Source
11.	Hsiao, W L	Oncogene	1990	USA	Comprehensive Cancer Center
					Columbia Univ., Health Sciences, NYC
12.	Johanning, G L	Nutrition and Cancer	1995	USA	Department of Nutrition
					Sciences, Univ. Alabama
13.	Kim, R S	Cancer Letters	1992	Netherlands	Department of Pharmacology
					and Therapeutics, Univ. of
					Manitoba, Faculty of Medicine.
14.	Noguchi, M	Oncology	1995	Switzerland	Department of Surgery,
					Kanazawa Univ. Hospital,
					School of Medicine, Japan
15.	Lambert, J D	Cancer Letters	2001	Ireland	Arizona Cancer Center, The
					Univ. Arizona, Tucson, AZ
16.	Palmantier, R	Cancer Research	1996	USA	Laboratory of Molecular
					Carcinogenesis, National Institute
					of Environmental Health Sciences,
					Research Triangle Park, North
					Carolina
17.	Reddy, N	Biochemical	1997	USA	Laboratory of Molecular
		Biophysiologic			Biophysics, NIEHS, Research
		Research			Triangle Park, North Carolina
		Communication			
18.	Rose, D P	Cancer Research	1990	USA	Division of Nutrition and
					Endocrinology, American
					Health Foundation, Valhalla, NY
19.	Sangeetha,	Cancer Letters	1992	Ireland	Department of Medicine,
	Sagar P.				Nizam's Inst. Of Med. Sciences,
					Punjagutta, Hyderabad, India
20.	Sathyamoorthy,	Cancer Research	1994	USA	Laboratory of Nutritional and
	N				Molecular Regulation, National
					Cancer Institute, NIH,
					Maryland
21.	Schultze-Mosgau	European Journal of	1998	England	MRC Toxicology Unit, University
	M H	Cancer			Leicester, U.K.

Table W: NDGA and Breast Cancer/Neoplasm Author Profiles

One possible explanation for the widely disseminated research interest in NDGA and breast cancer prevention, as demonstrated by journals of publication, countries of publication and affiliations of authors, is related to the use of NDGA in food preparation/preservation in 21 countries, and the continued limited use in the United States. NDGA has demonstrable safety, is

easily available, and could be inexpensively purchased by the consuming public as a functional food product. A discussion of these findings and implications for further studies follows Chapter V.

CHAPTER V

CONCLUSIONS

This chapter presents an overview of the significant findings of the study, an examination of those findings including implications of the study and recommendations for futher research. The purpose of the study was to establish whether there exists a content relationship between two complementary sets of literature, or conversely, to demonstrate the non-interactivity or disjointness of the literatures. The knowledge synthesis methodology of cocitation analysis was successfully used to disclose non-interactive, disjoints sets of literatures that shared complementary, logical connections. The sets of literature in this study were functional foods and nordihydroguairetic acid (the target literatures) and breast cancer (the source literature).

The broad content focus of this study was breast cancer as discussed in the public literature. Over one-half of the population is at risk for breast cancer. "An estimated 211, 300 new cases of invasive breast cancer are expected to occur among women in the United States during 2003. It is the most frequently diagnosed non-skin cancer in women. Breast cancer incidence rates have continued to increase since 1980, although the rate of increase slowed in the 1990's, compared to the 1980's" (American Cancer Society, 2003). This translates into an incidence rate of a new breast cancer diagnosis every 2 minutes. In addition an estimated 39,800 deaths are anticipated from breast cancer in 2003 (American Cancer Society, 2003). Treatment after discovery of breast cancer is minimally effective, and commonly very disfiguring and distressing for women. Prevention of breast cancer is the logically desirable avenue for research and application of knowledge.

A potential chemopreventative for breast cancer is nordihydroguaiaretic acid (NDGA). Nordihydroguaiaretic acid has been a focus of biomedical research for over 50 years.

Extensive investigations and listings of the properties and attributes of NDGA have been published, verified and accepted into the general scientific community. *In vitro* studies of NDGA have confirmed the properties of antigenotoxicity (Madrigal-Bujaidar, 1998), antimutagenic and antitumorigenic (Nakayama, 1992; Wang, 1991; Athar, 1990), and growth inhibition and apoptosis in human cancer cells (Seufferlein, 2002; Lambert, 2001). The more recent studies also continue to show no gross or organ specific toxicity (McCormick, 1987; Lambert, Meyers, Timmerman & Dorr, 2001; Seufferlein, Seckl, Schwartz, Beil, Wichert, Baust, et.al., 2002). Additionally, NDGA continues to be used in the food supply in 21 countries. Parallel research in defining surrogate biomarkers for chemopreventive agents has increased the potential for conducting meaningful chemoprevention trials, at a reduced cost and increased efficiency (Dhingra, 1993; Dhingra, 1995). The sums of these factors strongly support the need for *in vivo* research on breast cancer prevention with NDGA as a functional food.

Study Findings

The generic research question: "Can solutions to problems in one discipline be found in the literature of another discipline by finding unrecognized links between the literatures of the two disciplines?" has been answered in the affirmative for four of six research questions. The six research questions answered were:

1. Will cocitation analysis of the public literature on functional foods and nordihydroguaiaretic acid, exclusive of the breast cancer, reveal undiscovered connections?

   ANSWER: Yes, undiscovered connections were revealed.

2. Will cocitation analysis of the public literature on functional foods and nordihydroguaiaretic acid, exclusive of the breast cancer, reveal linkages of a

possible preventative agent?

ANSWER: Yes, NDGA as a functional food is a potential preventative agent.

3. Will cocitation analysis of the public literature on nordihydroguaiaretic acid and the public literature on breast cancer, reveal undiscovered connections?

   ANSWER: No, NDGA has been researched *in vitro*, for breast cancer treatment, therefore this is not an undiscovered connection. However, no research has been conducted on human beings with breast cancer, i.e., *in vivo*, even though the anti-tumor properties of NDGA have been known for more than 20 years.

4. Will cocitation analysis of the public literature on nordihydroguaiaretic acid and the public literature on breast cancer, reveal linkages of a possible preventative agent?

   ANSWER: Yes, NDGA is chemopreventive, *in vitro,* for human breast cancer cells.

5. Will cocitation analysis of the public literature on functional foods, nordihydro-guaiaretic acid and the public literature on breast cancer, reveal undiscovered connections?

   ANSWER: No, the connections are known. However, NDGA could be marketed as a functional food for prevention of breast cancer.

6. Will cocitation analysis of the public literature on functional foods, nordihydro-guaiaretic acid and the public literature on breast cancer, reveal linkages of a possible preventative agent?

   ANSWER: Yes, NDGA is chemopreventive for breast cancer in laboratory studies.

The research questions #3 and #5 were not confirmed. However, this result demonstrates the complementary nature of the sets of literatures and lends emphasis to the occurrence of parallel research without meaningful integration of findings from two related disciplines.

The research questions were also stated as formal hypothesis. The three hypotheses and answers are as follows:

> H_1: In the syllogistic paradigm of A intersection B, a literature search of the human and animal cell research with nordihydroguaiaretic acid will establish characteristics of nordihydroguaiaretic acid shared with functional foods.
>
> RESULT: Supported
>
> H_2: In the syllogistic paradigm of B intersection C, cocitation analysis of the nordihydroguaiaretic acid *in vivo* research literature and the breast cancer literature will reveal an absence of linkages, therefore disjointness of the literatures.
>
> RESULT: Supported.
>
> H_3: In the syllogistic paradigm of A intersection B intersection C, an undiscovered public knowledge phenomena will be explicated, i.e.,nordihydroguaiaretic acid is chemopreventative for breast cancer.
>
> RESULT: Supported.

The results of this study are consistent with D.R. Swanson's pioneering work in knowledge synthesis via bibliographic techniques. Swanson's methods can be used to identify non-interactive, disjoint literatures. Continuing support for his techniques has been demonstrated.

Implications

The findings in this study have implications for the information scientist. The knowledge synthesis methodology practiced by D.R. Swanson and replicated in this study uses the bibliometric research method of author cocitation analysis (ACA). The use of ACA in this context identifies sets of literatures that are logically but not bibliometrically related. The establishment of logically related but non-interactive literatures in this manner is predictive

research in bibliometric terms or retrodictive in some instances. D.R. Swanson's *oeuvre* of knowledge synthesis examples relate specifically to the biomedical literature. However, the techniques can be duplicated with other sets of health-related literatures in other disciplines, to uncover solutions to health problems and provide answers to prevention of disease and the treatment of illnesses. The disciplines of dietary science, agriculture, environmental science, genetics, human and plant biology closely relate and interconnect with the disciplines of biomedicine, alternative medicine and public health.

The information scientist can utilize the techniques in this study to produce new knowledge synthesis results. The establishment of a syllogistic model (or similiar logic paradigm), combined with the techniques of combinatorial keyword searching and author cocitation analysis can be applied in many scientific literature contexts. In this manner the information scientist could make valuable contributions to world health problems.

The implications for applying the study techniques in clinical practice are immeasurable. As the cost of treatment in healthcare rises and the consuming public is encouraged to practice preventative healthcare measures, intense efforts are needed in the disciplines of nutritional science and environmental science to produce research-based findings. Factors in the individual's dietary intake and environmental exposures are two major determinants of illness and disease. Development of new functional food consumer products advertised as promoting health and preventing disease are causing healthcare providers and practitioners in the biomedical field to focus on functional foods. Many functional foods are marketed without evidentiary research to substantiate their health benefit claims. This study could be replicated with other functional foods to test Swanson's techniques and provide linkages to studies.

Environmental exposures, both those that are known as in occupational exposures and unknown, as in distant-site airborne mercury exposures, are daily reminders of the collective effects of our world on the health of the population. In another dimension, the question arises as to the sufficiency in number of information scientists to address the volumes of potential information from such projects as the Human Genome Project. More bibliometric and informatics research studies are needed to establish connections caused by interruptions of DNA as manifest in disease and illness.

Recommendations for Further Study

The techniques of knowledge synthesis from publicly accessible databases can be the linch-pin for extended bibliographic research connections that could accelerate bench science discoveries. A database of bibliometric predictive research connections could be established to assist the process. Author cocitation analysis used in the search of logically related yet non-interactive sets of literature is a viable knowledge synthesis technique.

For example, further exposition of the functional foods area supports the need for more research. The functional food arena is a relatively new but burgeoning one, according to market research. Market research literature estimates U.S. sales of functional foods exceeded $18.2 billion in 2002, with an additional $7 billion spent on functional beverages (Leighton, 2002). Predictions of sales in function foods will exceed $32.7 billion by 2005. Timely research on functional foods is needed. In addition to market analysis articles, the functional food literature is highly focused on analysis and review articles with less documentation on research. This limits the acceptance of functional foods as effective chemopreventative agents and supports the need for information science research.

Summary

Swanson's conceptualization of undiscovered public knowledge phenomena allows for global exploration of topics. The refined techniques provide a viable model for knowledge synthesis by utilizing electronic databases and well-proven bibliographic techniques for retrieval and subsequent analysis. The syllogism provides the structure and defines the parameters for searching the specific sets of literature. Combinatorial keyword searching directs and delineates the retrievals. The search for an absence of linkages between sets of literature allows, and ultimately requires the researcher to be the final judge of relevance. Data collection without human analysis is just data; human analysis transforms data to information and potential knowledge.

This study supported Swanson's techniques of knowledge synthesis and in addition, extended the research model on two fronts. These two fronts were as follows:

1. Research was conducted which established positive linkages between the functional foods literature and the phytochemical nordihydroguaiaretic acid. These linkages were established by interpretation of biomedical research and knowledge of nutrition and food technology.
2. The linkages opened a 'window' to examine discrete, positive examples of undiscovered public knowledge. Specifically, the linkages were the first step in establishing disjointness or lack of connectivity between two bodies of literature and a third body of literature regarding the prevention of breast cancer.

The next step in correlating bibliometric research with biomedical research is to begin studies with humans. We need to start now with longitudinal studies developed for those women without breast cancer who are taking the potentially chemopreventative agent nordihydroguaiaretic acid.

APPENDICES

APPENDIX A

List of Functional Foods Which Inhibit Experimental Cancer

APPENDIX A

LIST OF FUNCTIONAL FOODS WHICH INHIBIT EXPERIMENTAL CANCER*		
Food Component	Food	Experimental Cancer Inhibited
Bifidobacterium longum cultures Calcium	Fermented dairy products	Colon, liver
Carotenoids B-carotene	Green/yellow vegetable, Fruits	Colon, stomach
Conjugated linoleic acid	Cheese, cooked meats	Breast, forestomach, skin
Diallyl sulfide	Garlic, onions	Esophagus, forestomach, large intestine, liver
Fiber	Cereal, bread	Breast, colon
Indole-3-carbinol (glucobrassicin)	Cruciferous vegetables	Breast, endometrium. Forestomach, liver, lung
Minerals Calcium Selenium	Dairy products Vegetable	Large intestine Breast, skin, large intestine, liver, lung
Monoterpenes D-carvone D-limonene	Caraway seed Citrus fruits Fish, poultry, dairy products	Forestomach, lung Breast, forestomach, lung Large intestine
Phenolics (glycosides) Catechins (-)Epigallocatechin-3-gallate	Fruits, vegetables, tea, coffee, cereal grains	Lung, skin, small intestine
Flavones Quercetin	Vegetables	Breast, colon
Isoflavones Genistein	Soy products	Breast, colon
Hydroxycinnamic acids Caffeic acid Chorogenic acid Ferulic acid	Fruits, vegetables, soy, cereals	Forestomach Large intestine, liver Forestomach
Tannins Tannic acid	Vegetables	Forestomach, lung
Ellagic acid	Fruits	Esophagus, liver
Protease inhibitors Bowman-Birk Edi ProA soy protein	Soy Soy	Liver Liver
Soy protein isolate	Soy	Breast

Food Component	Food	Experimental Cancer Inhibited
Thiocyanates (glucosinolates) Benzyl isothiocyanate	Broccoli, cabbage, Watercress	Breast, forestomach, liver, lung
Benzyl thiocyanante	Broccoli, cabbage, watercress	Breast, liver
Phenethyl isothiocyanate		Breast, esophagus, forestomach, lung
Sulforaphane		Breast
Vitamins Vitamin A Vitamin C (ascorbic acid) Vitamin E (a-tocopherol)	Liver, milk, eggs Citrus fruits, vegetables Seeds, nuts, vegetable and seed oils	Liver, lung Kidney, large intestine, lung, breast, forestomach, large intestine, oral, skin

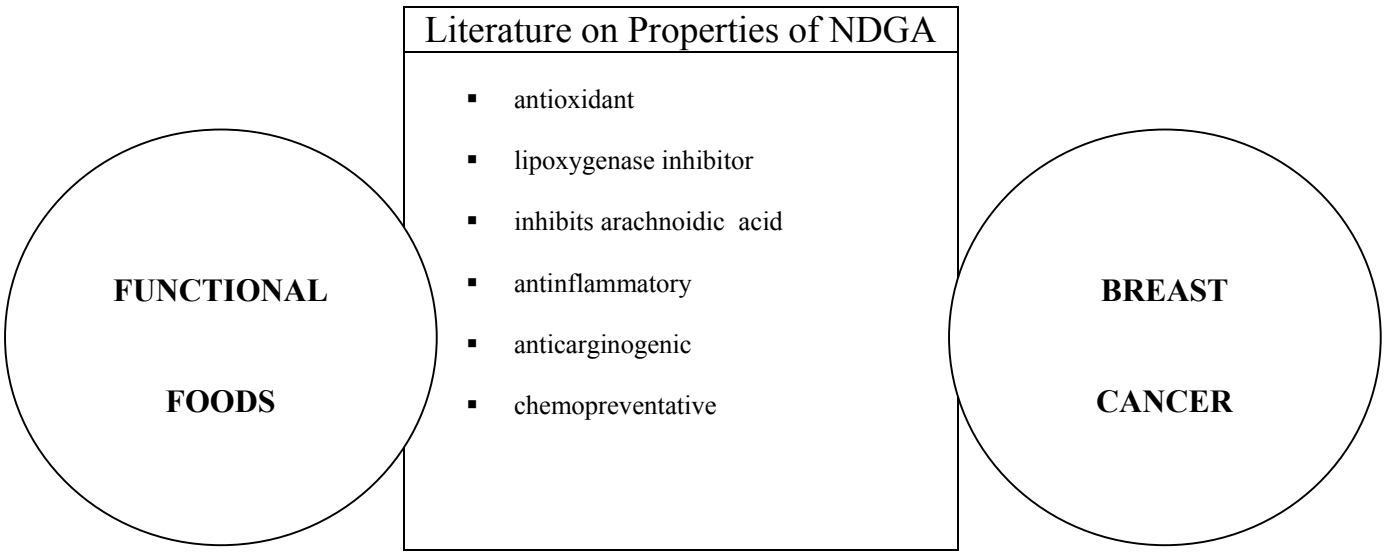
*From: Diet and Cancer: A Synopsis of Causes and Prevention Strategies, by G.M. Williams and E.L. Wynder. In: *Nutrition and Cancer Prevention,* R.Watson and S. Mufti, (Eds.), (1996).

APPENDIX B

Paradigmatic Scheme of Complementary but Disjoint Literatures

APPENDIX B

PARADIGMATIC SCHEME OF COMPLEMENTARY BUT DISJOINT LITERATURES



Target Literatures

Source Literature

APPENDIX C

Botanical Classification Systems for Cresote Bush, *Larrea divaricata*

APPENDIX C

Botanical Classification for creosote bush, *Larrea divaricata*

1. The PLANTS database of the USDA, Natural Resources Conservation Service, lists three scientific genera and four species for the common name plant 'creosote bush', and one genera as 'larrea' common name. Listed under the family 'Zygophyllaceae' are the following genera and species:

SCIENTIFIC NAME (GENERA AND SPECIES)	**COMMON NAME**
Larrea Cav.	larrea
Larrea tridentata (Sesse & Moc. ex DC.) Coville Synonym: Larrea maxicana Moric.	creosotebush
Larrea tridentata var. arenaria L Benson	creosotebush
Larrea tridentata var. tridentata (Sesse & Moc. ex.DC.) Coville Synonyms: Covillea tridentata (Sesse & Moc. Ex DC) Vail Larrea divaricata auct. Non Cav. Larrea glutinosa Engelm.	creosotebush

2. The Botantical Dermatology Database (BoDD) (1994) lists the following for the family Zygophyllaceae:

Larrea Synonym: Covillea	
Larrea divaricata Synonym: Covillea tridentata	Creosote Bush

3. The Fire Effects Information System (FEIS) of the the USDA Forest Service (1995), lists the following:

Larrea tridentata (D.C.) Cov. Synonym: Larrea divaricata Cav.	creosotebush

4. The PhytochemDB (USDA, Beckstrom-Sternberg, 1994) list the following:

Larrea tridentata (SESSE & Moc. ex. DC.) COV.	chaparral, creosote bush

APPENDIX D:

Dr. Duke's Phytochemical & Ethnobotanical
Database—Biological Activities of
Nordihydroguaiaretic Acid
&
Ethnobotanical Uses

Dr. Duke's Phytochemical and Ethnobotanical Databases

Biological Activities of NORDIHYDROGUAIARETIC-ACID

12-Lipoxygenase-Inhibitor; SAB;
5-Lipoxygenase-Inhibitor; CPB38:3054;
Allelopathic;
Allergenic; MAR;
Analgesic; 300-400 mg/man/day; AEH233;
Antiaggregant; LRN-AUG93;
Antibacterial; MIC=10 ug/ml; W&W;
Anticarcinogenic; LAF;
Anticonjunctivitic; LAF;
Antigalactagogue; LAF;
Antiinflammatory; BJP3:10;
Antimetabolite; LRN-AUG93;
Antimutagenic; DMD19:620;
Antioxidant; 100-200 mg/kg; AEG233;
Antioxidant; 5-100; UNE;
Antiseptic; W&W;
Antithyroid; JNM1:10;
Antitumor; DMD19:620;
Antiulcer; CPB38:3053;
Calcium-Antagonist; 50 uM; J15728;
Carcinogenic; PCF:69;
Cyclooxygenase-Inhibitor; SAB;
Cytotoxic; BJP3:10;
Fungicide; JBH;
Herbistat; ACS588:148;
Larvicide; LAF;
Lipoxygenase-Inhibitor; IC50=10-86 uM; JAF44:2057;
Lyase-Inhibitor; IC50=9-79 uM; JAF44:2057;
NADH-Oxidase-Inhibitor; BJP3:10;
Pesticide;
Phospholipase-Inhibitor; BJP3:10;
Phytotoxic;
Respiroinhibitor; LAF;

Ethnobotanical uses

Larrea tridentata (ZYGOPHYLLACEAE)

Antiseptic Standley; Arthritis Eb31: 348; Bruise Standley; Cancer(Stomach) Hartwell; Chafe Eb31: 348; Diarrhea Eb31: 348; Diuretic Altschul; Dysuria Altschul; Emetic Standley; Gastritis Standley; Hematochezia Eb31: 348; Intestine Standley; Knee Eb31: 348; Rheumatism Standley; Sore Eb31: 348, Standley; Tuberculosia Standley; Venereal Eb31: 348, Standley; Wound Standley

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* = Chemical(s) found in plant shown to be effective for the ailment medicated
** = Plant itself shown to be effective for the ailment medicated

APPENDIX E

Sample of Downloaded and Analyzed
Data on One Article

APPENDIX E

Sample of Downloaded and Analyzed Data on One Article

1. **Article downloaded from Biosis Previews©, from search on PHYTOCHEMICALS AND BREAST CANCER**:

1/9/1
13230970 Biosis No.: 200100438119
Suppression of aromatase (estrogen synthetase) by red wine phytochemicals.
Author: Eng Elizabeth T; Williams Dudley; Mandava Usha; Kirma Nimeer; Tekmal Rajeshwar Rao; Chen Shiuan(a)
Author Address: (a)Division of Immunology, Beckman Research Institute of the City of Hope, Duarte, CA, 91010: schen@coh.org**USA
Journal: Breast Cancer Research and Treatment 67 (2): p 133-146 May, 2001
Medium: print
ISSN: 0167-6806
Document Type: Article
Record Type: Abstract
Language: English
Summary Language: English
Abstract: Estrogen promotes the proliferation of breast cancer cells. Aromatase is the enzyme that converts androgen to estrogen. In tumors, the expression of aromatase is upregulated compared to surrounding non-cancerous tissue. In this study, we found that wine contains phytochemicals that are capable of suppressing aromatase. Red wine was shown to be much more effective than white wine in the suppression of aromatase activity. Whole wine, lyophilized wine, and heat-treated extracts were examined for aromatase inhibition in a human placenta microsomal assay. C18 Sep-Pak cartridge (Waters Co.) separation of red wine extracts under an increasing acetonitrile (ACN) gradient found that the most active components were in the 20% ACN fraction, in that they inhibited the wild-type human placenta aromatase, wild-type porcine placenta and blastocyst aromatase in a dose-dependent fashion. The 20% ACN active fraction was heat stable and inhibited aromatase in a non-competitive manner. The aromatase-inhibitory action of red wine extracts was also examined with a transgenic mouse model in which aromatase is over-expressed in the mammary tissues. It was found that the intake of the 20% ACN fraction by gavage completely abrogated aromatase-induced hyperplasia and other changes in the mammary tissue. This is the first report demonstrating that wine, especially red wine, contains phytochemicals that can inhibit aromatase.

Registry Numbers: 9039-48-9: AROMATASE; 9039-48-9: ESTROGEN SYNTHETASE
Descriptors:

Major Concepts: Nutrition; Tumor Biology
Biosystematic Names: Cricetidae--Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Hominidae-- Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae--Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Suidae--Artiodactyla, Mammalia, Vertebrata, Chordata, Animalia
Organisms: CHO cell line (Cricetidae)--Chinese hamster ovary cell line; human (Hominidae)--female, normal subjects, patient; mouse (Muridae)--transgenic animal model; pig (Suidae)--animal model, female
Biosystematic Classification (super Taxa): Animals; Artiodactyls; Chordates; Humans; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Primates; Rodents; Vertebrates
Diseases: breast cancer--in-vitro cell study, neoplastic disease, reproductive system disease/female
Chemicals & Biochemicals: aromatase {estrogen synthetase}--normal breast tissue activity, ovary cell activity, placental microsomal activity, rede wine phytochemical-induced activity suppression, tumor cell activity; red wine--20 percent acetonitrile fraction, aromatase inhibitory activity, tumor cell growth inhibitory activity
Methods & Equipment: mass spectrometry--analytical method, spectroscopic techniques--CB, spectroscopic techniques--CT
Alternate Indexing: Breast Neoplasms (MeSH)
Concept Codes:
02506 Cytology and Cytochemistry-Animal
02508 Cytology and Cytochemistry-Human
10802 Enzymes-General and Comparative Studies; Coenzymes
13202 Nutrition-General Studies, Nutritional Status and Methods
24004 Neoplasms and Neoplastic Agents-Pathology; Clinical Aspects; Systemic Effects
Biosystematic Codes:
85740 Suidae
86215 Hominidae
86310 Cricetidae
86375 Muridae

2. Cited reference search on SciSearch©, on author Eng E.:

4/9/1
10465073 **Genuine Article#:** 532FR **Number of References:** 100
Mechanisms of disease - Subtle acquired renal injury as a mechanism of salt-sensitive hypertension

Author: Johnson RJ (REPRINT) ; Herrera-Acosta J; Schreiner GF; Rodriguez-Iturbe B
Corporate Source: Baylor Coll Med,Div Nephrol,SM-1273,6550 Fannin St/Houston//TX/77030 (REPRINT); Baylor Coll Med,Div Nephrol,Houston//TX/77030; Inst Nacl Cardiol I Chavez,Dept Nephrol,Mexico City/DF/Mexico/; Scios,Sunnyvale//CA/; Univ Zulia,Univ Hosp Renal Serv,Maracaibo 4011//Venezuela/; Univ Zulia,Univ Hosp Dept Immunobiol,Maracaibo 4011//Venezuela/
Journal: NEW ENGLAND JOURNAL OF MEDICINE , 2002 , V 346 , N12 (MAR 21) , P 913-923
ISSN: 0028-4793 **Publication date:** 20020321
Publisher: MASSACHUSETTS MEDICAL SOC/NEJM , WALTHAM WOODS CENTER, 860 WINTER ST,, WALTHAM, MA 02451-1413 USA
Language: English **Document Type:** REVIEW
Geographic Location: USA; Mexico; Venezuela
Journal Subject Category: MEDICINE, GENERAL & INTERNAL
Identifiers-- KeyWord Plus(R): MUSCLE CELL-PROLIFERATION; BLOOD-PRESSURE VARIATION; ANGIOTENSIN-II; TUBULOINTERSTITIAL DISEASE; SYMPATHETIC OVERACTIVITY; MEDIATED HYPERTENSION; ARTERIAL-PRESSURE; IN-VIVO; SODIUM; RATS
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10405675 **Genuine Article#:** 521JP **Number of References:** 18
The effect of a church-based breast cancer screening education program on mammography rates among African-American women

Author: Husaini BA (REPRINT) ; Sherkat DE; Levine R; Bragg R; Cain V; Emerson JS; Mentes CM
Corporate Source: Tennessee State Univ,Ctr Hlth Res,Box 9580/Nashville//TN/37209 (REPRINT); Tennessee State Univ,Ctr Hlth Res,Nashville//TN/37209
Journal: JOURNAL OF THE NATIONAL MEDICAL ASSOCIATION , 2002 , V 94 , N2 (FEB) , P 100-106
ISSN: 0027-9684 **Publication date:** 20020200
Publisher: NATL MED ASSOC , 1012 10TH ST, N W, WASHINGON, DC 20001 USA
Language: English **Document Type:** ARTICLE
Geographic Location: USA
Journal Subject Category: MEDICINE, GENERAL & INTERNAL
Abstract: This study examines the effectiveness of breast cancer screening education programs on mammography rates among African-American women 40 years of age and over. We conducted two types of educational programs in community settings, primarily in African-American churches. Three-month follow-up interviews were used to determine whether women who participated in programming were more likely to get a mammogram if they had not had a mammogram in the last year. Our results demonstrate that the educational programs significantly increased the likelihood of getting a mammogram when compared to a control group that received no educational programming. Further, we found that the programs were effective for motivating breast cancer screening in housing projects as well as in the churches, and that the effectiveness of the programs remained even when we controlled for socioeconomic status, depression, and age.
Descriptors--Author Keywords: mammography ; African American ; cancer screening ; church-based
Identifiers-- KeyWord Plus(R): MINORITY WOMEN; BLACK-WOMEN; OLDER; STRATEGY
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10364293 **Genuine Article#:** 519CQ **Number of References:** 57
Syndecan-4 up-regulation in proliferative renal disease is related to microfilament organization

Author: Yung S; Woods A; Chan TM; Davies M; Williams JD; Couchman JR (REPRINT)
Corporate Source: Univ Alabama,Dept Cell Biol,Birmingham//AL/35294 (REPRINT); Univ Alabama,Dept Cell Biol,Birmingham//AL/35294; Univ Wales Coll Med,Inst Nephrol,Cardiff CF4 4XN/S Glam/Wales/; Univ Hong Kong,Dept Med Div Nephrol,Hong Kong/Hong Kong/Peoples R China/
Journal: FASEB JOURNAL , 2001 , V 15 , N7 (MAY 29) , P U218-U237
ISSN: 0892-6638 **Publication date:** 20010529
Publisher: FEDERATION AMER SOC EXP BIOL , 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA
Language: English **Document Type:** ARTICLE
Geographic Location: USA; Wales; Peoples R China
Journal Subject Category: BIOCHEMISTRY & MOLECULAR BIOLOGY; BIOLOGY; CELL BIOLOGY
Abstract: Syndecan-4 is a transmembrane heparan sulfate proteoglycan (HSPG) expressed widely in mammalian cells. It has been implicated in growth-factor binding, cell-extracellular matrix adhesion, and tissue damage responses. Although several HSPGs are present within kidney mesangium and glomerular basement membranes, no data are available on the synthesis of syndecan-4 by mesangial cells or its expression in human renal disease. We examined renal biopsy specimens from normal controls, nonproliferative disease (thin-membrane disease), and progressive proliferative disease (IgA nephropathy). By using RT-PCR and immunohistochemical staining, we identified an increase in both gene expression (IgA nephropathy vs. thin membrane disease, P = 0.0004) and synthesis of syndecan-4 in progressive proliferative disease. Syndecan-4 increased within both mesangium and tubulo-interstitium, as did alpha-actinin, a microfilament cytoskeletal component. Syndecan-4 was a focal adhesion component in human mesangial cells, colocalizing with vinculin and alpha-actinin, and was present in the cortical, submembraneous myosin sheath as seen for alpha-actinin. Both syndecan-4 and alpha-actinin were retained selectively in detergent-resistant cytoskeleton-matrix preparations, emphasizing their close association in cell-matrix adhesion. Syndecan-4 may be important in the adhesion, migration, and proliferation of HMC, and its up-regulation could indicate proliferative disease.
Descriptors--Author Keywords: proteoglycans ; heparan sulfate ; actin ; alpha-actinin
Identifiers-- KeyWord Plus(R): HEPARAN-SULFATE PROTEOGLYCANS; PROTEIN-KINASE-C; IGA NEPHROPATHY; DIABETIC NEPHROPATHY; CYTOPLASMIC DOMAIN; BASEMENT-MEMBRANE; MESANGIAL CELLS; IN-VITRO; EXPRESSION; ADHESION
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10199354 **Genuine Article#:** 497TL **Number of References:** 17
Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism

Author: Mazzali M (REPRINT) ; Hughes J; Kim YG; Jefferson JA; Kang DH; Gordon KL; Lan HY; Kivlighn S; Johnson RJ
Corporate Source: Baylor Coll Med,Div Nephrol,1275 Smith,6550 Fannin St/Houston//TX/77030 (REPRINT); Baylor Coll Med,Div Nephrol,Houston//TX/77030; Univ Washington,Med Ctr Div Nephrol,Seattle//WA/98195; Queen Mary Hosp,Hong Kong/Hong Kong/Peoples R China/; Merck Inc,W Point//PA/
Journal: HYPERTENSION , 2001 , V 38 , N5 (NOV) , P 1101-1106
ISSN: 0194-911X **Publication date:** 20011100
Publisher: LIPPINCOTT WILLIAMS & WILKINS , 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA
Language: English **Document Type:** ARTICLE
Geographic Location: USA; Peoples R China

Journal Subject Category: PERIPHERAL VASCULAR DISEASE
Abstract: An elevation in circulating serum uric acid is strongly associated with the development of hypertension and renal disease, but whether uric acid has a causal role or whether it simply indicates patients at risk for these complications remains controversial. We tested the hypothesis that uric acid may have a causal role in the development of hypertension and renal disease by examining the effects of mild hyperuricemia in rats. Mild hyperuricemia was induced in rats by providing a uricase inhibitor (oxonic acid) in the diet. Hyperuricemic rats developed elevated blood pressure after 3 weeks, whereas control rats remained normotensive. The development of hypertension was prevented by concurrent treatment with either a xanthine oxidase inhibitor (allopurinol) or a uricosuric agent (benziodarone), both of which lowered uric acid levels. Blood pressure could also be lowered by reducing uric acid levels with either allopurinol or oxonic acid withdrawal. A direct relationship was found between blood pressure and uric acid (r=0.75, n=69). with a 10-mm He, blood pressure increase for each 0.03-mmol/L (0.5-mg/dL) incremental rise in serum uric acid. The kidneys were devoid of urate crystals and were normal by light microscopy. However, immunohistochemical stains documented an ischemic type of injury with collagen deposition, macrophage infiltration, and an increase in tubular expression of osteopontin. Hyperuricemic rats also exhibited an increase in juxtaglomerular renin and a decrease in macula densa neuronal NO synthase. Both the renal injury and hypertension were reduced by treatment with enalapril or L-arginine. In conclusion, mild hyperuricemia causes hypertension and renal injury in the rat via a crystal-independent mechanism, with stimulation of the renin-angiotensin system and inhibition of neuronal NO synthase.
Descriptors--Author Keywords: uric acid ; hypertension, renal ; renin-angiotensin system ; nitric oxide
Identifiers-- KeyWord Plus(R): CARDIOVASCULAR-DISEASE; ESSENTIAL-HYPERTENSION; EVENTS; RISK
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APPENDIX F

Annotated Bibliography of Functional Foods and NDGA Documents

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Annotated Bibliography of Functional Foods and NDGA Documents

1. Blalock, J E.(1981). Anticellular and immunosuppressive activities of foodborne phenolic compounds. Proceedings of the Society for Experimental Biology and MedicineSociety. 167(3), 391-392.

   Several phenolic compounds, including nordihydroguaiaretic acid, were examined for their ability to inhibit *in vitro* antibody production and tumor cell clone formation. The results showed phenolic compounds commonly found in foods or food additives inhibit tumor cell clone formation, thus have antitumor activity.

2. Garreau, B. (1991). Phytoestrogens: New ligands for rat and human alpha-fetaprotein. Biochimica et Biophysica Acta. 1094 (3), 339-345.

   Nordihydroguaiaretic acid (NDGA) is described as one lignan and phytoestrogen that binds estrone and estadiol to rat alpha-fetoprotein (AFP) and binds unsaturated fatty acids to both rat and human AFP. NDGA may play a role in AFP-dependent normal and pathological growth and development.

3. Harper, A. (1999). Antioxidant effects of isoflavonoids and lignans, and protection against DNA oxidation. Free Radical Research. 31(2), 149-160.

   Nordihydroguaiaretic acid is tested as a potent antioxidant with hydroxyl radial-scavenging, iron chelating and DNA-binding activity, and support is suggested for its proposed role as a natural cancer-protective agent.

4. Martin, M E. (1996). Interactions between phytoestrogens and human sex steroid binding protein. Life Science. 58 (5), 429-436.

   Nordihydroguaiaretic acid was researched for its sex steroid binding protein (SBP) activity. The results indicate that this phytoestrogens may modulate SBP activity and so influence the role of this protein in the delivery of hormonal information to the sex steroid-dependent cells.

5. Morikawa, M., Fukuchi, K., Inoue, E. & Tsuboi, M. (1992). Effect of mammalian lignans on fMLP-induced oxidative bursts in human polymorphonuclear leukocytes. *Journal of Pharmacy and Pharmacology.* 44(10), 859-861.

   The inhibitor effects of nordihydroguaiaretic acid were investigated, and endogenous lignans were tested as to their effect on leukocytes.

6. Park, S. (1998). Inhibition of fos-jun-DNA complex formation by dihydroguaiaretic acid and in vitro cytotoxic effects on cancer cells. Cancer Letters (Ireland). 127 (1-2),

23-28.

Research reported which showed dihydroguaiaretic acid and nordihydroguaiaretic acid suppressed leukemia, lung cancer and colon cancer in an *in vitro* bioassay. The probable mechanism is inhibition of fos-jun-DNA complex formation.

7. Sathyamoorthy, N. (1994). Stimulation of pS2 expression by diet-derived compounds. Cancer Research (United States). 54 (4), 957-961.

The estrogen-responsive protein pS2 in estrogen receptor-positive MCF-7 breast cancer cells were assayed. Results indicated nordihydroguaiaretic acid was able to elicit an estrogen-like response.

8. Schegg, K. M. (1984). The effect of nordihydroguaiaretic acid and related lignans on formyltetrahydrofolate synthetase and carboxylesterase (cellular enzymes) activity.Biochimica et Biophysica Acta. 788 (2), 167-180.

The ability of nordihydroguaiaretic acid (NDGA) and other lignans to inhibit enzyme activity was evaluated. NDGA was a potent enzyme inhibitor.

9. Schottner, M. (1998). Lignans interfering with 5 alpha-dihydrotestosterone binding to human sex hormone-binding globulin. Journal of Natural Products. 61 (1), 119-121.

This is a report on inhibition of 5 alpha-dihydrotesterone (DHT) to the human sex-binding globulin (SHBG), and may have implications for hormone dependent tumor growth.

10. Schultze-Mosgau, M.H. (1998). Regulation of c-fos transciption by chemopreventive isoflavonoids and lignans in MDA-MB-468 breast cancer cells. European Journal of Cancer. 34 (9), 1425-1431.

Nordihydroguaiaretic (NDGA) and isoflavonoids were tested and compared for their ability to interfere with mitogenic and tumor promotional signal transduction pathways. NDGA has some ability to interfere with signal transduction.

APPENDIX G

Annotated Bibliography of NDGA and Breast Cancer Documents

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Annotated Bibliography of NDGA and Breast Cancer Documents

1. Ara, G. & Teicher, BA. (1996). Cyclooxygenase and lipoxygenase inhibitors in cancer therapy. *Prostaglandins, Leukotrienes and Essential Fatty Acids.* 54(1), 3-16.

   The article reviews the mechanism of action and types of tumors affected by cyclooxygenase and lipoxygenase inhibitors. NDGA is included as active against mammary tumors.

2. Buckman, DK., Hubbard, N. & Erickson, K.(1991). Eicosanoids and linoleate-enriched growth of mouse mammary tumor cells. *Prostaglandins, Leukotrienes and Essential Fatty Acids.* 44(3), 177-184.

   The research reports on the contrast between lipoxygenase and cyclooxygenase metabolites as inhibitors of linoleate. Results indicate that lipoxygenase metabolites, including NDGA, are probably more effective.

3. Cunningham, DC, Harrison, L. & Shultz, T. (1997). Proliferative responses of normal human mammary and MCF-7 breast cancer cells to linoleic acid, conjugated linoleic acid and eicosancid synthesis. *Anticancer Research.* 17(1A), 197-203.

   NDGA was included in research examining the role of linoleic acid and conjugated linoleic acid on mammary tumors. NDGA showed growth suppression with MCF-7 cells.

4. Damtew, B & Spagnuolo, R. (1997). Tumor cell-endothelial cell interactions: Evidence for roles of lipoxygenase products of arachidonic acid in metastasis. *Prostaglandins, Leukotrienes and Essential Fatty Acids.* 56(4), 295-300.

   NDGA partially inhibited adhesion of breast cancer cells to endothelial cells, thus it may have a role in reducing breast cancer cell metastasis.

5. Earashi, M, Noguchi, M & Tanaka, M. (1996). *In vitro* effects of eicosanoid synthesis inhibitors in the presence of linoleic acid on MDA-MB-231 human breast cancer cells. *Breast Cancer Research and Treatment.* 37(1), 29-37.

   Research suggested that the growth of MDA-MB-231 breast cell lines *in vitro* is affected by both lipoxygenase and cyclooxygenase products.

6. Earashi, M., Noguchi, M., Kinoshita, K. & Tanaka, M. (1995). Effects of eicosanoid synthesis inhibitors on the *in vitro* growth and prostaglandins E and leukotriene B secretion of a human breast cancer cell. *Oncology.* 52(2), 150-155.

   Research demonstrated the inhibitory effect of cyclooxygenase and lipoxygenase metabolites on a human breast cancer cell line. Several products, including NDGA, suppressed cell growth and secretion of other adverse metabolites.

7. Earachi, M, Endo, Y., Obata, T., Minami, M., Noguchi, M., Miyazaki, I. & Sasaki, T. (1996). Effects of linoleic acid and eicosanoid synthesis inhibitors on the growth and c-myco oncogene expression of human breast cancer cells. *International Journal of Oncology.* 8(1),145-151.

   Research reports on the effects of linoleic acid and eicosanoid synthesis inhibitors on the growth, DNA synthesis, and *c-myc* oncogene expression of human breast cancer cell lines.

8. Fulton, AM., Lattera, J.& Hanchin, C. (1989). Prostaglandin E2 receptor heterogeneity and dysfunction in mammary tumor cells. *Journal of Cell Physiology.* 139(1), 93-97.

   An early report on the dissimilar or diverse reaction of prostaglandin E2 receptor cells on mammary tumor cells. Study suggests there are implications for growth of normal mammary cells.

9. Harper, A., Kerr, D., Gescher, A. & Chipman, J. (1999). Antioxidant effects of isoflavonoids and lignans and protection against DNA oxidation. *Free Radical Research.*31(2), 149-160.

   NDGA is reported for its potent antioxidant activity on hepatocytes and a breast cancer cell line.

10. Hofmanova, J., Musilova, E. & Kozubik, A. (1996). Suppression of human cancer cell proliferation by lipoxygenase inhibitors and gamma-radiation *in vitro*. *General Physiology and Biophysics.* 15(4), 317-431

    Arachidonic acid inhibition activity and radiation on a human breast carcinoma cell line and on monocytes was investigated. Inhibition of growth by these chemicals and radiation may be an improved technique to suppress growth.

11. Hsiao, WL, Pal, H., Matsui, M. & Weinstein, I. (1990). Effects of specific fatty acids on cell transformation induced by an activated c-H-ras oncogene. *Oncogene.* 5(3), 417-421.

This is an investigation of the mechanisms by which dietary lipids influence the carcinogenic process in rat fibroblasts.

12. Johanning, GL. & Lin, T. (1995). Unsaturated fatty acid effects on human breast cancer cell adhesion. *Nutrition and Cancer.* 24(10), 57-66.

This article reports on nutrient modulation and its effect on human breast cancer cell adhesion.

13. Kim, RS.,Zaaborniak, C, Begleiter, A. & LaBelle, F. (1992). Antiproliferative properties of aminosteroid antioxidants on cultured cancer cells. *Cancer Letters.* 64(1), 61-66.

The antiproliferative property of three aminosteroid antioxidants was examined in this research. The conclusion indicates the effects of these antioxidants in cancer cells may be part due to an interaction with glucocorticoid receptors.

14. Noguchi, M, Rose, DP, Earashi, M. & Miyazaki, I. (1995). The role of fatty acids and eicosanoid synthesis inhibitors in breast carcinoma. *Oncology.* 42(4), 265-271.

This article reviews literature on the role of fatty acids and eicosanoid synthesis inhibitors on breast carcinoma. The exact mechanisms remain undiscovered.

15. Lambert, JD, Meyers, R, Timmerman, B, & Dorr, R. (2001). tetra-O-methylnordihydroguaiaretic acid inhibits melanoma *in vivo. Cancer Letters.* 171(1), 47-56.

The research reports the ability of NDGA to inhibit various cancer types *in vitro* and *in vivo*.

16. Palmantier, R., Roberts, J, Glasgow, W, Eling, T. & Olden, K. (1996). Regulation of the adhesion of a human breast carcinoma cell line to type IV collagen and vitronectin: Roles for lipoxygenase and protein kinase. *Cancer Research.* 56(9), 2206-2212.

This report explores the ability of lipoxygenase inhibitors to regulate adhesion of breast cancer cells.

17. Reddy, N, Everhart, A., Eling, T. & Glasgow, W. (1997) Characterization of a 15-lipoxygenase in human breast carcinoma BT-20 cells: Stimulation of 13-HODE formation by TGF alpha/EGF. *Biochemical Biophysical Research Communications.* 231(1), 111-116.

This research describes the conversion of linoleic acid and arachidonic acid in human breast cells, and suggests a link between their metabolism and growth factor regulation of cell proliferation in a breast cancer cell line.

18. Rose, DP. & Connolly, J. (1990). Effects of fatty acids and inhibitors of eicosanoid synthesis on the growth of a human breast cancer cell line in culture. *Cancer Research.* 5(922), 7139-7144.

    This research suggests indicate that MDA-MB-231 cell growth is dependent on leukotriene rather than prostaglandin production.

19. Sangeetha, Sagar P, Das, UN, Koratkar, R, Ramesch, G, Padma, M. & Sravan, K. (1992). Cytoxic action of cis-unsaturated fatty acids on human cervical carcinoma (HeLa) cells: Relationship to free radicals and lipid peroxidation. *Cancer Letters.* 63(3), 189-198.

    The article reports further study on free radicals as the mediators of the tumoricidal action of fatty acids. It suggests the mechanism of their production may be different in different types of tumor cells.

20. Sathyamoorthy, N., Wang, T. & Phang, J. (1994). Stimulation of pS2 expression by diet derived compounds. *Cancer Research.* 54(4), 957-61.

    This article explores mechanisms for the lowered risk for hormone-dependent cancers among vegetarians. The researchers develop an assay to screen for compounds with estrogenic-like activity.

21. Schultze-Mosgau, MH, Dale, I., Gant, T, Chipman, J., Kerr, D. & Gescher, A. (1998). Regulation of c-fos transcription by chemopreventive vs. isoflavonoids and lignans in MDA-MB-468 breast cancer cells. *European Journal of Cancer.* 34(9), 1425-1431.

    This research examines the effect of several isoflavonids and lignans on their ability to interfere with mitogenic and tumour promotional signal production.

GLOSSARY

GLOSSARY OF TERMS

A

1. antioxidant: A substance that inhibits oxidation or reactions promoted by oxygen or peroxides (Merriam-Webster's Nineth New Collegiate Dictionary, 1991). Any substance that prevents or reduces damage caused by reactive oxygen species (ROS) or reactive nitrogen species (RNS). ROS and RNS are highly reactive chemicals that attack other molecules and modify their chemical structure Antioxidants are commonly added to foods to prevent or delay their deterioration due to exposure to air. (Awasthi, Singhal & Awasthi, 1996).
2. antitumorigenic: Substance or agent capable of preventing tumor formation; substance may affect cells directly to prevent tumor formation, or affect transformed cells themselves, i.e., formed tumor cells (VERIS, 1999).
3. arachidonic acid: An essential dietary component for mammals. The free acid is the precursor of biosynthesis of prostaglandins, thromboxanes, hydroxyeicosatetraenoic acid derivatives including leucotrienes and is thus of great biological significance (On-Line Medical Dictionary, 1997-2003).
4. autooxidation: Refers to the spontaneous reaction between atmospheric oxygen and many types of organic compounds; this process is affected by light, heat, concentration of oxygen, moisture, and the presence of catalysts or inhibitors (Jadhav, Nimbalkar, Kulkarni & Madhavi, 1996).

C

5. carcinogenesis: The process of tumor development; the generation of cancer from normal cells (On-Line Medical Dictionary, 1997-2003).
6. carcinogens: Substances that increase the risk of neoplasms in humans or animals. Both genotoxic chemicals, which affect DNA directly, and nongenotoxic chemicals, which induce neoplasms by other mechanisms, are included (On-Line Medical Dictionary, 1997-2003).
7. chemopreventative agent: Nutritive or nonnutritive food component being scientifically investigated as a potential inhibitor of carcinogenesis for primary and secondary cancer prevention (Greenwald, 1996).
8. cocitation (or co-citation): A form of document coupling, which describes the frequency with which two documents are cited together; the situation in which two (or more) authors, documents, or journals are simultaneously cited by another document (Diodato, 1994).
9. covillea tridentata: See *Larrea divaricata;*
10. cresote bush: Common name for the *Larrea divaricata* shrub.

D

11. dietary supplements: Products in capsule, tablet or liquid form that provide essential nutrients, such as a vitamin, an essential mineral, a protein, an herb, or similar nutritional substance (Minkwitz, 1999).
12. designer food: Processed foods that are supplemented with food ingredients naturally rich in disease preventing substances. This may involve genetic engineering of food (Vanconcellos, 1998)

E

13. eicosanoids: Endogenous bioactive substances in human tissues which are derived from the precursor arachidonic acid, and function in the body to……; includes the metabolites prostaglandin, leukotrienes, and thromboxane. Eicosanoids have been detected in many different human tissues including the central nervous system and human brain tumors (Price, 1994).

F

12. free-radical chain reaction: A linked reaction involving free radicals, which are atoms or groups of atoms that have at least one unpaired electron, which makes them highly reactive; free radicals promote beneficial oxidation that produces energy and kills bacterial invaders; in excess, they produce harmful oxidation that

can damage cell membranes and cell contents (Jadhav, Nimbalkar, Kulkarni & Madhavi, 1996).

13. functional foods: (a) Foods containing components that have demonstrated protective effects against several disease processes, such as cancer and cardiovascular disease; functional foods have anticarcinogenic effects in experimental systems (Williams & Wynder, 1996); (b) Foods with physiologically active components, both from plant (phytochemicals) and animal (zoochemicals) sources, including natural and modified food ingredients, that may provide a health benefit beyond the traditional nutrients it contains; (c) any modified food or food ingredient that may provide a health benefit beyond the traditional nutrients it contains (Milner, 2000).I
14. *in vitro:* Within a glass, observable in a test tube, in an artificial environment (Merriam-Webster's Nineth New Collegiate Dictionary, 1991).
15. *in vivo:* Within the living body (Merriam-Webster's Nineth New Collegiate Dictionary, 1991).
16. isomeric: Having the same percentage composition; said of two or more different substances which contain the same ingredients in the same proportions by weight (On-Line Medical Dictionary, 1997-2003).

L

17. *Larrea divaricata:* A plant species from the family *Zygophyllaceae*, which grows as a shrub indigenous to some of the southwestern state, i.e., Texas, Nevada, New Mexico, Utah, Arizona, and Mexico, and into parts of South America; also known as *Larrea tridentata* and *Covillea tridentata.* Common name is creosote bush; derives the common name from an abundance of resinous coating on the leaves and small twigs which, when burned, yields black smoke and a rank odor resembling creosote; shrub also known as "el gobernadora", "hideonodo", "hediondilla", and "chaparral" (Downum, 1998; Mabry, 1949);
18. *Larrea tridentata:* Probably same as *Larrea divaricata*, and frequently both names are interchanged.
19. leukotrienes: A family of hydroxyeicosotrienenoic (HETE) acid derivatives in which the lipid moiety is conjugated to glutathione or cysteine. Members of the group are potent pharmacological mediators, for example SRS A, the slow reacting substance of anaphylaxis (Price, 1994).
20. lignan: A plant phenolic compound, closely related to lignins, which are widespread throughout the plant kingdom and either help to defend against various pathogens or act as antioxidants in flowers, seeds, seed coats, stems, nuts, bark, leaves, and roots(Croteau, Kutchan & Lewis, 2000).
21. lignin: A substance characterizing wood cells and differing from cellulose in its conduct with certain chemical reagents. Note: Recent authors have distinguished four forms of this substance, naming them lignose, lignin, lignone, and lignireose. Older alternate, noun: A complex polymer; the chief non-carbohydrate constituent of wood; binds to cellulose fibers to harden and strengthen cell walls of plants (Croteau, Kutchan & Lewis, 2000).
22. lipoxygenase: Enzyme that catalyses the oxidative conversion of arachidonic acid to the hydrooxyeicosenoic acid (HETE) structure in the synthesis of leucotrienes (Price, 1994).
23. lipoxygenase inhibitor: compounds or agents that combine with lipoxygenase and thereby prevent its substrate-enzyme combination with arachidonic acid and the formation of the eicosanoids products hydroxyeicosatetraenoic acid and various leukotrienes (Price, 1994)

M

24. meso compound: A compound that has two or more chiral centers but does not rotate plane-polarized light because it has an internal plane of symmetry. These compounds are identical to their mirror images (On-Line Medical Dictionary, 1997-2003)

N

25. NDGA: Nordihydroguaiaretic acid (see below).
26. nordihydroguaiaretic acid: [NDGA]. A naturally occurring product of the lignan family, *Zygophyllaceae*, nordihydroguaiaretic acid is a crystalline phenol extracted from the leaves, twigs and branches of the plant species *Larrea divaricata* (or *Larrea tridentata*) (Duke, 2001). NDGA is a potent antioxidant, lipoxygenase inhibitor and anticarcinogenic agent.

27. nutraceuticals: Any substance that may be considered a food or part of a food and provides medical or health benefits, including the prevention and treatment of disease (Vasconcellos, 1998).

O

28. optically active: A material which can rotate plane-polarized light (On-Line Medical Distionary, 1997-2003).

P

29. pharmafood: Food or nutrient that claims medical or health benefits, including the prevention and treatment of disease (Vasconcellos, 1998).
30. phenomena: Pleural used as singular, for phenomenon (Merriam-Webster's Nineth New Collegiate Dictionary, 1991).
31. phenolic compounds: The term 'phenolic' or 'polyphenolic' can be defined chemically as a substance which possesses an aromatic ring bearing one or more hydroxyl substituents, including functional derivatives (esters, methyl ethers, glycosides, etc.). Most phenolics have two or more hydroxyl groups and are bioactive substances occurring widely in food plants that are eaten regularly by substantial numbers of people. Lignans are one class of phenolic compounds (Croteau, Kutchan & Lewis, 2000).
32. phytochemical: Substances found in edible fruits and vegetables that may be ingested by humans daily in gram quantities and that may exhibit a potential for modulating human metabolism in a manner favorable for cancer prevention; Phytochemicals are naturally occurring biochemicals that give plants their color, flavor, smell and texture; currently the term is being used only for those plant chemicals that may have health-related effects but are not considered essential nutrients such as proteins, carbohydrates, fats, minerals, and vitamins (Croteau, Kutchan & Lewis, 2000).
33. phytopharmacognacy: A subfield of pharmacology which studies natural drugs (primarily plant origin), including the study of their biological and chemical components, botanical sources, and other characteristics (economic, biochemical, biological, etc.). The study is called phytopharmacognosy. (Wilkerson, 2000).
34. prebiotics: A nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or limited number of bacteria in the colon (Roberfroid, 1998).
35. probiotics: Live microbial feed supplements which beneficially affect the host animal by improving its intestinal microbial balance. Antibiotics and other related compounds are not included in this definition. In humans, lactobacilli are commonly used as probiotics, either as single species or in mixed culture with other bacteria. Other genera that have been used are bifiobacteria and streptococci (Roberfroid, 1998).
36. prostaglandins: Any of a class of hormone-like, regulatory molecules constructed from polyunsaturated fatty acids such as arachidonate. These molecules participate in a number of functions in the body, such as smooth muscle contraction and relaxation, vasodilation, and kidney regulation (Price, 1994).

R

37. racemic: Of, relating to, or constituting a compound or mixture that is composed of equal amounts of dextrorotatory and levorotatory forms of the same compound and is not optically active (Merriam-Webster Nineth New Collegiate Dictionary, 1991).
38. thromboxanes: Physiologically active compounds found in many organs of the body. They are formed *in vivo* from the prostraglandin endoperoxides and cause platelet aggregation, contraction of arteries, and other biological effects. Thromboxanes are important mediators of the actions of polyunsaturated fatty acids transformed by cyclooxygenase (Price, 1994).

Glossary terms are from: *On-Line Medical Dictionary©*, a medical dictionary *(©*CancerWeb 1997- 2003, CancerWeb Project, Academic Medical Publishing, U.K., http://cancerweb.ncl.ac.uk/omd/), the Merriam Webster Nineth New Collegiate Dictionary (1991) and various cited references as indicated.

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