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Health Benefits and Biological Activity of Ginger Phytochemicals Against Chronic Diseases and Cancers

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ABSTRACT

As cancer prevalence escalates significantly across the globe, fighting this terminal illness using phytochemicals is considered a green anticancer therapeutic approach. Many plants contain useful bioactive compounds that can influence cancer remedies positively. Moreover, these bioactive compounds derived from natural sources exhibited great vital contribution activities such as antioxidant, anti-inflammatory, and antimicrobial. Since antiquity, ginger was used in folk medicine as a reason for its ability to relieve systemic pain and food flavoring. Along with recent findings and discoveries, ginger and its derived phenolic compounds such as 6-gingerol, 8-gingerol, and 10-gingerol, shogaol, parasols, zingerone, and α-curcumene, each independently or collectively is well known to contribute prospectively in an accessible way in many chronic conditions such as obesity, diabetes, non-alcoholic fatty liver disease, Alzheimer disease, rheumatoid arthritis, asthma, and chronic kidney disease. On the other hand, drug-based ginger's pharmacological properties show significant suppression of specific cancers such as skin, colorectal, pancreatic, prostate, breast, lung, AML, gastric, and HCC through series of distinctive mechanisms. It is notably now that these ginger characteristics, along with its beneficial flavonoid contents, are a novel therapeutic approach in a variety of ailments.

Keywords- Anticancer, Bioactive components, Ginger phytochemicals.

I. INTRODUCTION

Cancer prevalence: a life-threatening nightmare

Cancer is a disease group that characterizes abnormal cell growth and spread in one's body. It is the second principal cause of numerous deaths worldwide [1]. Not much information on the risk factors is fully understood yet; however, latest knowledge, as described by Song Wu et al., subjected that the prospective causes of this illness include exposure to radiations, chemical carcinogenesis, tumor-causing viruses, smoking, obesity, biological aging and abnormalities of genetics [2]. As shown by GLOBOCAN 2020, cancer new incidence statistics estimate roughly 19,292,789 million of the world population. The mortality rate accounts for approximately 9,958,133 million of the total incidences. Although there are several cases of cancer, lung cancer occupies the top position in the list as the most frequent cancer type in males followed by prostate cancer. Whereas in females, breast cancer dominates the prime number of cases [3]. To compare these statistics with cancer cases in 2012, the cumulative rise in the number of cases considered significant. Both statistics have shown identical common types of cancer in both genders

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[4].

The fight against high cancer mortality rate is increasingly prospering; this is observed in high-income countries where people tend to spend generously on cancer control and prevention. The impact on middle and low-income countries is painful; thereupon, the application of early detection, followed by a treatment plan might have potentially saved human lives [5].

The anti-cancer therapeutic strategy has attracted significant attention, but chemotherapy and radiotherapy were the standard treatment regimen for cancer. An example of a new method of treating tumors is anti-angiogenesis, which promises an effective treatment modality. The benefit of using an angiogenesis inhibitor combined with radiotherapy found to be protecting blood vessels against radiation-lured the damage of cells [6].

Many numbers of research and studies have been conducted to find a useful therapeutic agent derived from plant "ginger" as a potential anticancer and its medical benefits [7]–[10].

In this article, a brief discussion takes place to look for an alternative way to use phytochemical derived from plant "ginger" and see the outcomes of using it as anticancer against different cancer types.

II. GINGER PHYTOCHEMICALS

Historically, conventional medicine was based on plants and beneficial byproducts in treating the vast majority of diseases. The modern medical system revolutionizes a successful enhancement of overall people's health. Even though modern medicines have undesirable side effects, the curative advantages are quite useful in such emergencies. Nevertheless, finding other natural sources such as plants to obtain medical benefits considered valuable. As far as medical benefits originated from natural compounds are a concern, such compounds can be modified structurally to get synthetic molecules, which, according to modern studies, have proven unprecedented curative quality. Nowadays, plants pharmaceutical properties set a significant quantum leap forward in terms of an anticancer agent of these plants' derivatives [11], [12]. Consequently, plant phytochemicals have possibly made significant involvement in cancer remedy [13]. In addition to the stated, the development of medicaments-based natural sources is less expensive compared with synthetic compounds [14], which may introduce some toxicity [15].

Ginger (*Zingiber officinale* Roscoe), family (*Zingiberaceae*) [7], which is a flowering perennial plant rich in beneficial nutrients such as vitamin B, vitamin C, resins, acids, and folic acid manganese and magnesium. For centuries, ginger has been commonly used for a variety of purposes, for instance, as a flavoring agent. It consists of volatile oils, which gives a fragrance and taste, and as a herbal medicinal agent [16], [17].

In the early stages, folk medicine, "as the name suggests," is the treatment of disease or injury supported traditional way, especially on oral tradition, instead of relying on modern scientific practice and sometimes utilizing indigenous plants as remedies. The lack of affordability to get modern medicine, especially for those who are living in villages, folk medicine comes as the fundamental method of treatment [18].

Table 1: Estimated Number of New Cancer Incident Cases Worldwide, Deaths, 5- Years Prevalence, Both Sexes, All Ages in 2020.

	NEW CASES				DEATHS				5-YEARS PREVALENCE	
Cancer	**Number**	**Rank**	**(%)**	**Cum.risk**	**Number**	**Rank**	**(%)**	**Cum.risk**	**Number**	**Prop. (per 100000)**
Breast	2,261,419	1	11.7	5.2	68,496	4	6.9	1.49	7,790,717	201.58
Lung	2,206,771	2	11.4	2.74	1,796,144	1	18	2.18	2,604,791	33.42
Prostate	1,414,259	3	7.3	3.86	375,304	8	3.8	0.63	4,956,901	126.13
Colon	1,148,515	4	6	1.3	576,858	5	5.8	0.55	3,045,225	39.07
Stomach	1,089,103	5	5.6	1.31	768,793	3	7.7	0.9	1,805,968	23.17
Liver	905,677	6	4.7	1.11	830,180	2	8.3	1.01	994,539	12.76
Rectum	732,210	7	3.8	0.91	339,022	10	3.4	0.37	2,066,732	26.51
Cervix uteri	604,127	8	3.1	1.39	341,831	9	3.4	0.82	1,495,211	38.69
Oesophagus	604,100	9	3.1	0.78	544,076	6	5.5	0.68	666,388	8.55
Thyroid	586,202	10	3	0.68	43,646	25	0.44	0.05	1,984,927	25.46
Bladder	573,278	11	3	0.64	212,536	14	2.1	0.18	1,720,625	22.07
Non-Hodgkin	544,352	12	2.8	0.62	259,793	12	2.6	0.27	1,544,488	19.81

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lymphoma										
Pancreas	495,773	13	2.6	0.55	466,003	7	4.7	0.51	379,958	4.87
Leukaemia	474,519	14	2.5	0.5	311,594	11	3.1	0.32	1,340,506	17.2
Kidney	431,288	15	2.2	0.52	179,368	16	1.8	0.2	1,207,547	15.49
Corpus uteri	417,367	16	2.2	1.05	97,370	20	0.98	0.22	1,415,213	36.62
Lip, oral cavity	377,713	17	2	0.46	177,757	17	1.8	0.22	959,248	12.31
Melanoma of skin	324,635	18	1.7	0.37	57,043	23	0.57	0.06	1,092,818	14.02
Ovary	313,959	19	1.6	0.73	207,252	15	2.1	0.49	823,315	21.3
Brain, CNS	308,102	20	1.6	0.35	251,329	13	2.5	0.3	837,152	10.74
Larynx	184,615	21	0.96	0.25	99,840	19	1	0.13	518,380	6.65
Multiple myeloma	176,404	22	0.91	0.21	117,077	18	1.2	0.13	450,579	5.78
Nasopharynx	133,354	23	0.69	0.16	80,008	22	0.8	0.1	382,507	4.91
Gallbladder	115,949	24	0.6	0.13	84,695	21	0.85	0.09	137,466	1.76
Oropharynx	98,412	25	0.51	0.13	48,143	24	0.48	0.06	258,543	3.32
Hypopharynx	84,254	26	0.44	0.11	38,599	26	0.39	0.05	132,717	1.7
Hodgkin lymphoma	83,087	27	0.43	0.09	23,376	28	0.23	0.02	281,112	3.61
Testis	74,458	28	0.39	0.14	9,334	34	0.09	0.02	296,686	7.55
Salivary glands	53,583	29	0.28	0.06	22,778	29	0.23	0.03	160,292	2.06
Anus	50,865	30	0.26	0.06	19,293	30	0.19	0.02	141,378	1.81
Vulva	45,240	31	0.23	0.09	17,427	31	0.18	0.03	135,892	3.52
Penis	36,068	32	0.19	0.09	13,211	33	0.13	0.03	102,157	2.6
Kaposi sarcoma	34,270	33	0.18	0.03	15,086	32	0.15	0.01	82,033	1.05
Mesothelioma	30,870	34	0.16	0.03	26,278	27	0.26	0.03	37,047	0.48
Vagina	17,908	35	0.09	0.04	7,995	35	0.08	0.02	44,613	1.15
All cancer sites	**19,292,789**	**-**	**-**	**20.44**	**9,958,133**	**-**	**-**	**10.65**	**50,550,287**	**648.5**

Source: *International Agency for Research on Cancer GLOBOCAN 2020* [3].

III. GINGER CHEMISTRY

Looking at the chemistry of ginger, fresh roots of ginger have a wide range of chemical compounds, just like in many other spices. Some of the compounds found in ginger include zingiberene, which happens to be the most dominant going up to 30% of the essential oil in roots. Other compounds that contribute to the attribute flavor in ginger encompass are curcumin and ß-sesquiphelandrene. The availability of gingerols is responsible for the pungency [19]. In gingerol, the 6-gingerol compound happens to be one of the culprits. This specific compound is such a detached capsaicin compound that brings out the spiciness in chilies and piperine, which is present in black paper. Besides, 6-gingerol has been found to have the upper hand in medicine as an anti-tumor [20]. This specific compound has portrayed to possess an anti-angiogenic effect in cancer models and laboratory condition.

The compound inhibits explicitly new blood cells from being formed. To spread, tumor requires the generation of new blood cells. It is therefore valid that 6-gingerol proves useful in tumor treatment.

Most importantly, most of the research conducted has been in mice and very few in human models. The results are promising in mice, which calls for more research in human models to verify the outcome. Laboratory tests in humans have shown that shogaol has the possibility of inhibiting ovarian cancer [21]. Ginger is a famous spice that is used across the world and more so in Asian nations. After chemically analyzing ginger, results portray that ginger has more than 400 various compounds. The significant elements of the rhizomes of ginger are carbohydrates, accounting

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for an average of 60%, lipids accounting for about 6% and phenolic, and terpenes. Terpene elements of ginger encompass paradols, gingerol, and shogaol. Gingerols and shogaol are present in more gigantic proportions of 24% and 21% percent than the others [22].

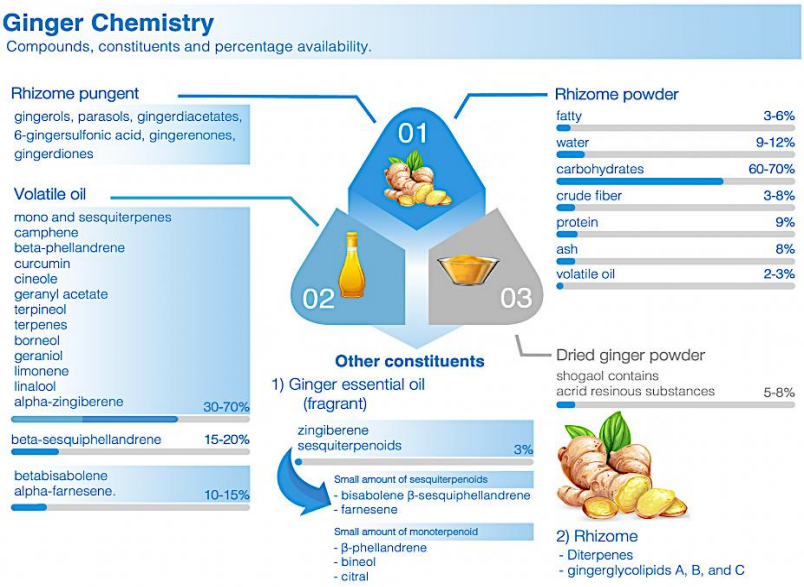

Figure 1: Ginger Chemistry: compounds, constituents, and percentage availability

Source: *Information adapted from (Karunakaran & Sadanandan, 2019); Zingiber officinale: Anti-inflammatory Actions and Potential Usage for Arthritic Conditions* [23]. *(This figure has been designed using images from Freepik.com)*

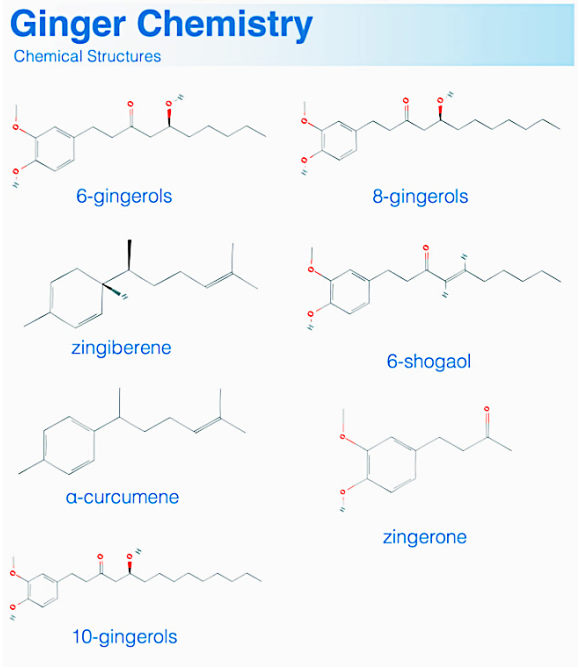

Figure 2: Chemical compounds of 6-gingerols, 8-gingerols, 10-gingerols, zingiberene, 6-shogaols, zingerone, and α-curcumene

IV. HEALTH BENEFITS OF GINGER

There are several documented benefits of ginger to the human body. First, the problem associated with some of the non-prescription anti-nausea drugs is that it acts through the body's central nervous system. For this reason, sleepiness or drowsiness is often causes an undesirable side effect [24]. Upon using ginger, sleepiness is rarely becoming a problem [25]. It has also shown to aid with the anesthetic response. Controlled studies showed that taking less than one gram of ginger capsule dose before the operation significantly reduced postoperative nausea [26]–[28].

Most health professionals, however, prevent ginger consumption before surgery because it led to lessening the platelet aggregation, which contributes to an increased bleeding disorder [29].

Irrespectively, the ability to control nausea has many advantages. For example, in a person with motion sickness, a single gram of ginger powder can reduce the occurrence of postoperative nausea and vomiting (PONV), motion sickness, and patients undergoing chemotherapy treatment [30].

The anti-inflammatory effects of ginger

Another health benefit of ginger is utilized in the prevention of chronic discomfort, a common ailment in millions of people. Because ginger contains an anti-inflammatory component, it can relieve pain indirectly by lowering the inflammation severity. What happens is that prostaglandins, natural inflammatory response compounds, are reduced, which relieves the pain [31]. Interestingly, many massage therapists will use ginger oil for this reason. For muscle and joint pain caused by rheumatoid arthritis (RA) or even athletes, ginger oil given daily can provide a potential enhancement in relieving pain [32].

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Experiments conducted using ginger bioactive components on various chronic phase of diseases/conditions:

Numerous studies have proven that ginger and its important compounds make a significant contribution in one way or another to treating, inhibiting, or reducing side effects of some non-carcinogenic chronic conditions.

Implying that ginger is a rich source of suitable and effective nutraceuticals, for instance, in the rat study, the ethanolic ginger extract found to lower the blood glucose level. Also, ginger ameliorable to lower both serum cholesterol and triglycerides levels in hyperlipidemic and diabetic rats. Other areas in which ginger supplement and extract had proven its effectiveness are seen in insulin resistance, fatty liver condition, adipose tissue, and kidney injury [33].

In this review, we managed to recapitulate as many experiments being conducted utilizing ginger on various diseases/conditions:

1- Diabetes Mellitus

DM is a heterogeneous group of disorders characterized by hyperglycemia, glycosuria, and associated abnormalities of lipid and protein metabolism. The lack of insulin secretion is an abnormal DM metabolism that occurred due to the destruction of beta-cells in the islets of Langerhans [34]. In 2016, the trend in mortality rate attributed to this chronic condition was roughly 1.6 million. In 2014, nearly 422 million people worldwide suffered from this terminal ailment [35].

Toward the discovery of ginger compounds influence as an anti-diabetic agent, a research conducted by Wei et al. found that 6-shogaol and 6-paradol are both played a key role in lowering the glucose level in an in-vivo mouse model [36]. Likewise, an investigation carried out by Fajrin et al. on a condition, where diabetes involved in it, called painful diabetic neuropathy (PDN) revealed that 6-shogaols and other ginger extracts alleviated pain symptoms of P.D.N. Similarly, studies have also reported that ginger phenolic compounds participated in lowering the hyperglycemic condition in type II DM [37]. A study conducted by Ebrahimzadeh et al. indicated that ginger supplementation lower fasting blood sugar, HbA1C and in patients with type 2 diabetes mellites [38].

2- Rheumatoid Arthritis

RA is an autoimmune inflammatory disease of arthropathy, distinguished by severe joint pain, deformity, and destruction [39]–[41]. RA is the most prevalent autoimmune disease with incompletely known reasons [42], [43]. RA's global prevalence is roughly estimated >19 million cases [44]. Funk et al. have conducted two experimental studies on ginger, on RA, in their previous research, they used the ginger crude extract to examine its anti-inflammatory response against RA in an animal model, the result showed positive effect against joint swelling, acute and chronic phase of arthritis. In addition to that, they managed to take an additional step by using other bioactive compound derived mainly from ginger known as ginger essential oils (GEO) in their second experiment, their findings exhibited that treatment using GEO has substantially inhibited the chronic phase of arthritis [45], [46]. Moreover, Aryaeian et al. claimed that ginger powder capable of enhancing RA by reducing apparent disease symptoms with distinctive gene expressions [47]. Chandra et al. have demonstrated ginger extract loaded nanoemulgel for the treatment of RA, which found to minimize the adverse effects of oral administration of nonsteroidal anti-inflammatory drugs (NSAIDs) as well as controlling the drug delivery process for a better constant release via nanoemulgel-loaded ginger extract. The usage of nanoemulgel achieves a principal beneficial way in the drug delivery system, which provides a prompt deeper penetration under its nanosize (ten-hundred nanometer) thus, allowing for an excellent drug delivery efficiency [48].

3- Obesity

Around the globe, obesity and its health-related risks became a real concern [49]. The prevalence and morbidity trend is in rising; therefore, severe actions along with these risks should be taken to reduce this disease in which representing in community awareness, dietary control, avoidance of high calories meals, physical sports practice, and medicine-induced gaining weight [50].

World Health Organization (WHO) described the term “obesity” as it is an excessively amassed abnormal fat that might develop a dangerous impact on human health [51]. Obesity likely occurs due to either factor defect, effect, or simultaneously a linkage between lack of exercise, genetic, environmental, food overconsumption, and lifestyle [52]. In 2016, over 650 million adults suffered from obesity of a total of 1.9 billion overweight adults [53]. Overweight and obese are terms best evaluated by measurement using body mass index (BMI), which is the relation between weight and height, and it merely calculated as (weight in kg/height in m^2), result ≥30 kg/m^2 defined obese [54]. In contrast, overweight ranges from (25 kg/m^2 up to 29 kg/m^2) [55], and healthy individual adults ranges from (18.5-20 kg/m^2 up to 24.9 kg/m^2) [56]–[58].

The medical complications of obesity may increase the risk development of type 2 diabetes mellitus[59], coronary heart disease [60], renal disease [61], and certain cancer types [62].

A positive effect of ginger-targeted obesity and other metabolic disorders successfully conducted by Wang et al. found that a specific dose of ginger supplementation showed considerable modifications in mice's gut microbiota, thus positively influencing obesity, insulin resistance, and liver functions and on minor inflammation grade [63]. Significant advantages have been claimed using herbal-based remedies in improving lipid metabolism, reducing fat accumulations in hepatocytes and adipocytes, and controlling the

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expression of adipogenesis-related genes. As suggested by Sayed et al., using a combination of (Ginger, Chinese Hawthorn, Red Pepper, Cinnamon, and Lotus Leaf) and their useful active components as anti-obesity are believed to treat lipid metabolism [64]. In addition to the state, one of the extracts rich in the benefits attained from ginger is ginger water, which obtained by freeze-drying rhizome at -60°C, was investigated in rats, results revealed a reduction in weight gain, prevention of obesity, and amelioration in glucose metabolism [33].

4- Non-alcoholic fatty liver disease

NAFLD is a chronic manifestation of the liver with a metabolic disorder identified by more than 5% fat accumulated in hepatocytes. It is commonly associated with a disturbance of insulin resistance metabolism with no history of alcohol consumption. The liver can develop severe disorders that begin from chronic NAFL, which becomes advance progressively into non-alcoholic steatohepatitis (NASH). NASH may further extend to cirrhosis, hepatic fibrosis, and hepatocellular carcinoma (HCC) [65]. Certain risk factors are associated with the occurrence of NAFL, such as cardiovascular disease (CVD), which is the primary cause of mortality, insulin resistance, and obesity [66]. The induction of obesity and type II DM metabolic disorders, particularly in NAFLD, presented a second vital lead to mortality globally [67].

The role of ginger in the treatment of NAFLD is investigated, confirmed results have established in NAFLD remedy as indicated by Rafie et al., that receiving 1500 mg of ginger for 12 weeks improves patients with NAFLD. Besides, the effect of gingerol and zerombon in response to inflammation is remarkable; they inhibited the level of C-reactive protein (CRP) active phase and TNF-α gene by reducing NFκB activity.

Additionally, in their randomized clinical trials study, showed that ginger supplement lowers ALT, total cholesterol, LDL, FBS, and insulin resistance index (HOMA), hs-CRP, as well as fetuin-A levels [68]. Similarly, these findings agree with those of Rahimlou M et al. [69]. Moreover, the hepatoprotective activity of ginger combined with silymarin provided evidence to reduce the severity of hepatic cirrhosis and fibrosis [70].

5- Alzheimer disease

AD is a neurological disease-affected brain tissue results in aging disorder with severe implications on cognitive ability and memory disturbance. Elderly populations are at the high-risk onset of dementia caused by AD. AD progresses over time; as a result, impairment in cognitive abilities, thinking, behavior, as well as failure to recognize and use ordinary things in daily life are observed. The pathological features of AD include an accumulation in amyloid-ß (Aß) protein results in senile plaques and acetylcholine (Ach) deficiency [71].

Medicinal properties of phenolic phytocompounds of dry ginger extract potentially act as antioxidants and anti-amyloidogenic in AD through two actions: inhibition or dissociation of Aß protein toxicity [72].

Besides, Karam AM et al. showed that the ginger phenolic compounds such as gingerols, shogaols, and paradols are protective agents in AD therapy [71]. Moreover, the number of studies are carried out regarding AD and other age-related neurological disorders (ANDs), which include Parkinson's disease (PD), stroke, neuro inflammation, neuronal apoptosis, oxidative stress using the therapeutic ability of ginger phytochemicals such as 6-gingerol, 6-shogaol, 6-paradol, zingerone and dehydrozingerone [73].

The action of gingerol in AD, as described by El Halawany et al., in their experiment, found that gingerol ameliorated the memory impairments in sporadic Alzheimer's disease (SAD) in a mouse model, while inhibits the COX-2 overexpression. Also, COX-2 overexpression due to streptozotocin (STZ) induced SAD injected in mice led to a decrease in the level of alpha-secretase while increasing the levels of beta and gamma secretases [74].

6- Asthma

Asthma is a chronic inflammatory condition that obstructs the air passage affecting the lung functions. It is characterized by typical known respiratory disease manifestations such as shortness of breath, wheezing, chest tightness, and cough [75], [76].

Known risk factors for the development of asthma etiology include obesity, genetics, smoking, family history of allergic-induced asthma, and bacterial/viral respiratory infections. The predominant risk factor that increases the early childhood-onset asthma is a parental history of atopic diseases. These risks vary in triggering asthma onset between childhood and adulthood [77]. Furthermore, air pollution exposure is known to progress the onset of asthma, becoming a crucial contributor to increasing mortality rate [78], [79].

Treatment is driven by ginger, and its anti-inflammatory properties have shown high mitigation in allergic asthma. A recent study carried out by Yocum et al. on the murine asthma model demonstrated the potential of ginger extract and 6-shogaol in the alleviation of the pathogens-related lung functions, airway hyper-responsiveness, and airway smooth muscle (ASM) relaxation [80]. Also, in a clinical trial study, ginger extract revealed appropriate regulator of inflammatory biomarker syntheses such as interleukin (IL)-4, IL-5 and IL-13, IL-25, and IL-33, as well as Th2, Th17 cells associated in the airway [81]. In agreement, the suppression of Th2-mediated immune response reduces allergic asthma [82].

7- Chronic Kidney Disease

CDK is a degenerative disorder with a high rate of morbidity and mortality with no known cure. Adults with diabetes and high blood pressure are more prone to it [83]. There is a disproportionate burden of chronic kidney disease in low- and middle-income countries, due to the fact that they are less capable of dealing with its

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consequences [84].

An individual with chronic kidney disease is defined by a decreased glomerular filtration rate (GFR) (<60 ml/min/1.73 m^2) or markers of kidney damage e.g., albuminuria, the most common marker, lasting over 3 months. CGA classifications are based on cause, glomerular filtration, and albuminuria criteria [85].

A study conducted by Irshad F, Munawar S, Rasheed A used ginger extract to treat diabetic nephropathy in albino rats. They injected rats with Alloxan (150 mg/kg body weight) intraperitoneally to induce diabetes. In the other diabetic group, ginger aqueous extract (200 mg/kg body weight) was given for five weeks. They observed a lower increase in Glomerular Mesangial matrix histologically than the other experimental groups [86]. In another study, peritoneal dialysis patients who received 1000 mg ginger daily showed reduced fasting glucose levels, a factor linked to diabetes, cardiovascular disease, and diabetic nephropathy [87]. Furthermore, an experimental study on mice showed that 6-shogaol protects against diabetic nephropathy, the leading cause of chronic kidney disease [88].

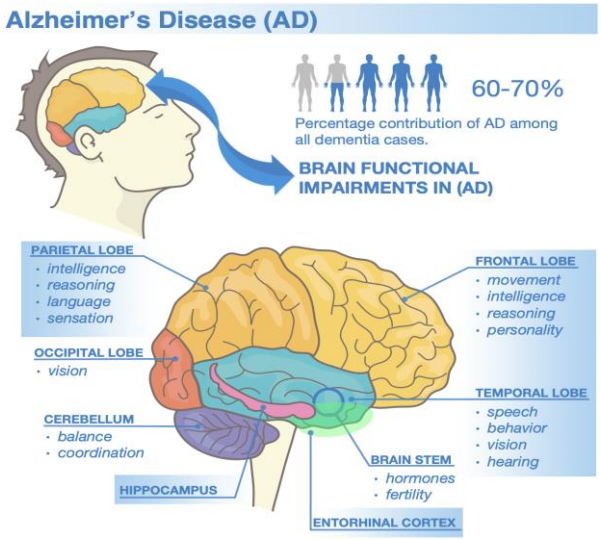

Figure 3: Brain functional impairments in Alzheimer's disease

V. GINGER BIOACTIVE COMPOUNDS

Plenty of bioactive components derived from fresh ginger-like gingerol, which is a polyphonic compound, is understood to possess a superb contribution to several biological activities like anticancer, antimicrobial, anti-inflammatory, and antioxidant. The usage method of ginger in treatment utilizes by different conditions: fresh, dried, fried, or carbonized. Examples of polyphenols derived from gingerol are 6-gingerol, 8-gingerol, and 10-gingerol. Furthermore, shogaol is a transformation state of gingerol based on temperature or storage for an extended period [89]. Gingerol is the most abundant constituent of ginger [90]. Another example of bioactive compounds of ginger are parasols, zingerone [91], and α-curcumene [92].

Ginger phytochemicals mechanism toward various cancers

In the sort of extraction, isolation, and experimental studies of those compounds, ginger derivatives present suggestive connection of biological activity in terms of anticancer and other activities mentioned above by the divergences mechanisms [93].

Successful medical studies exhibited the usefulness of ginger phytochemicals as anticancer are mentioned concisely in table 2.

Basing on evidence from epidemiological, in vitro and animal studies show that ginger and its useful components slow down the growth of cancer and induce the apoptosis of several kinds of cancer for instance ovarian, skin, breast, colon, oral, renal, gastric, pancreatic, prostate, brain and liver cancer [94]. These attributes of ginger and its components may be related to anti-inflammatory, antioxidant, and antimutagenic characteristics and several other biological processes.

Table 2: Mechanisms of Action of Various Ginger Phytochemicals in Different Cancer Types.

Phytochemical	Specific cancer suppressed	Mechanism	Ref
Ethanolic ginger extract	• Skin tumor (*In-vivo* experiment on mouse skin).	• Inhibits T.P.A. thus caused induction in the activity of epidermal ornithine decarboxylase, cyclooxygenase, and lipoxygenase.	[95]
6-Shogaol	• Breast cancer	• Reduced expression of MMP-9 by inhibiting cell invasion	
6-Gingerol	• Colorectal • Pancreatic • Prostate • Breast	• Cell death (apoptosis) is stimulated through the regulation of NAG-1 and the G1 cell cycle.	[95], [96]
8-Gingerol	• Colorectal	• Inhibiting cell proliferation by targeting EGFR signaling.	[97]

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Aqueous extract of ginger	• Gastric	• Antioxidant enzymes in the stomach aid in reducing oxidative stress. • Reduces the level of the following pro-inflammatory markers (TNF-α, NF-κB, PGE2, IL-6).	[98]
10-Gingerol	• Breast	• Apoptosis and cell cycle arrest are stimulated in triple-negative breast cancer cells.	[99]
Aqueous Crude Extract	• Acute Myeloid Leukemia *(In-vitro* experiment on HL60/ADR cell line).	• Decreasing cell viability. • Initiates apoptotic cell death.	[100]
Ethanolic ginger extracts (*Enhanced with the induction of ethanolic extracts of A*.C.).	• Hepatocellular carcinoma *(In-vitro* experiment on Huh-7 and HepG2 cell line).	• Inhibiting the growth of cancerous cells. Initiation of cell cycle arrest at the G2/M phase • Initiation apoptotic cell death of HepG2 and Huh-7.	[101]
β-element (*With the induction of Hyperthermia therapeutic method*).	• Lung *(In-vitro* experiment on NSCLC cell line A549).	• Inhibiting cell proliferation. • Decreasing S phase. • Initiates apoptotic cell death of A549 cells. • Promotes an increase in P21 and Baxproteins expression and decreases in caspase-9, Bcl-2, and survivingene expression.	[102]
Pure 6-shogaol	• Breast cancer • **A549** non-small cell lung cancer cells	• Inducing paraptosis in triple negative breast cancer (CCRF-CEM).	[103]
Ginger extract *(Combination with methotrexate MTX)*	• **B-ALL** cell lines • **ALL** primary cells	• Exhibiting synergistic effects on CCRF-CEM, Nalm-6 and acute lymphoid leukemia primary cells.	[104]
6-gingerol, zingerone and sesquiterpenes *Extracted from Ginger essential oil*	• **A549** lung carcinoma cell line • **HepG2** human liver cancer cell line • **MDA-MB-231** human breast cancer cell line	• Inducing features of apoptosis, anti-proliferation and cytotoxicity.	[105]
Ginger Rhizomes powder	• **MCF-7** human breast cancer cell lines • **MD A-MB-231**	• Inducing cytotoxic effects.	[106]
Ethanol Ginger Extract	• **MCF-7** human breast cancer cell line • **PANC-1** human pancreas carcinoma	• Inducing cytotoxic and apoptotic effects.	[107]

TPA: 12-Otetradecanoylphorbol-13-acetate, MMP-9: Matrix metalloproteinase-9, NAG-1: Nonsteroidal anti-inflammatory drug activated gene-1, EGFR: Epidermal growth factor receptor, NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells, TNF-α: Tumor necrosis factor alpha, IL-6: Interleukin 6, PGE2: Prostaglandin E2, AC: Antrodia cinnamomea, NSCLC: Non-small cell lung cancer, P21: cyclin-dependent kinase inhibitor, Bax: Bcl-2-associated X protein, Bcl-2: B-cell lymphoma 2 apoptosis suppressor gene.

Progression and development of tumors tend to be a sophisticated process with several steps that include metabolic and genetic changes [108]. Previous studies have analyzed medicinal plants in the management of diseases by modulating several biological processes like cancer. Ginger and its components portray essential effects in the management of the development of tumors via up-regulating the gene of suppressor of a disease, inactivation of VEGF, and the induction of apoptosis. As an angiogenic agent, VEGF plays a significant role in the progression and development of a tumor [109]. Thus, inhibiting VEGF is rendered a useful step in the management and prevention of growth of tumors. Earlier research shows that 6-gingerol plays a vital role in suppressing transforming, inflammatory, and hyperproliferation processes that are involved in various steps of carcinogenesis, metastasis, and angiogenesis. Other studies have shown that 6-gingerol and the components of ginger have an essential task in inducing apoptosis in prostate cancer through increasing p53 expression and reducing Bcl-2 appearance. Extant research also shows that 6-school reveal anticancer activities against breast cancer through the inhibition of invasion of the cell and the reduction of matrix

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metalloproteinase expression [110]. Past crucial research has suggested that 6-gingerol has a stimulating effect on apoptosis via upregulation of NAG-1 and an impact on G1 cell cycle arrest via downregulation of cyclin D1.

VI. COMBINATION OF GINGER COMPOUNDS WITH CHEMOTHERAPEUTIC AGENTS

Even though chemotherapy has proved successful, it has consistently shown inadequacy in the management of diseases because of its debilitating aftermath that arises from its severe non-specific effects on healthy cells. To add to that, the progress in chemoresistance coming from mono-targeting most of the time leads to the cessation of chemotherapy [111]. This calls for urgent development and execution of multi-targeted option therapies with minimum side effects or none at all. One promising approach that remains untapped is the augmenting of preventive chemotherapy using dietary extracts or phytochemicals. Ginger has a role in the depository of many bio-active elements that target cancer cells and helps mitigate side effects associated with chemotherapy. As a result, combination therapy involving ginger phytochemicals and chemotherapeutic agents is probably to offer efficacy with reduced toxicity [112]. This reveals the remarkable and the ignored potential and benefits of ginger phytochemicals in cancer management, the possibility of coming up with ginger-based combinational therapies, and crucial roadblocks with approaches to break them in clinical inventions translation.

Ginger is a renowned spice, especially for its attributes like pungent taste and aromatic fragrance that have healing properties that have been documented. Studies in Asia and Africa have shown that ginger is traditionally used in cancer management. The scientific society is probing further into the extraction of ginger components like gingerols, zingiberene, zingerone, and shogaols [113]. The therapeutics and mechanisms of ginger and its compounds is based on the following: cytotoxic effect on cancer cell lines, combination therapy with phenolic and chemotherapeutic compounds, enzyme inhibiting action, possible association with the microbiome and finally the application of nano-formulation of ginger compounds as more performing drug delivery approach in therapy of cancer.

VII. CONCLUSION

Ginger beneficial compounds have undergone many experimental studies, such as clinical trials and animal models. Potent bioactivities derived from ginger have significant attributions in treatment towards the vast majority of diseases. Ginger can trigger different roles in medicine, such as mitigating, inhibiting, stimulating, initiating, alleviating, increasing, decreasing, inducing, and other useful functions. Ginger and its constituents have critical properties in the treatment of many different types of cancer suggested that it is a remarkable, safe, and alternative utilization tumorigenic remedy. Thus, it is being considered a vital therapeutic plant. As with the discoveries obtained so far from studies and research that have proven effective in treating diseases and have helped to improve health, more experiments are needed to be conducted not only on ginger but also on other types of plants will contribute significantly to discovering other phyto nutraceutical properties.

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