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Genistein Derivatization - From a Dietary Supplement to a Pharmaceutical Agent

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1. Introduction

Many soy supplements in the market focus on estrogen and antioxidant properties of isoflavonoid, genistein. Due to the structural similarity to estrogen and binding to estrogen receptor, genistein is often referred to as a phyto-hormone or a dietary estrogen from soy. Target applications of isoflavone-enriched whole soy concentrates include natural hormonal replacement therapy and women's health products (Knight & Eden, 1996; Messina, 1995). However, beneficial effect of genistein on human health extends to the prevention of cancer, cardiovascular events, diabetes, and incidence of inflammatory diseases and management of some metabolic diseases (Birt et al., 2001, Kurzer, 2002; Rimbach et al., 2008; Węgrzyn et al., 2010).

The view of genistein as a safe and healthy food supplement is not entirely clear, however. Although most studies show no risk of high consumption of soy-based products for human growth, development or reproduction, there are some data urging caution in genistein overdose. Genistein is implicated as a possible cause of infertility and liver disease in some animal species. Consumption of genistein-rich food and supplements during pregnancy have been suggested to increase the risk of infant leukemias (Hengstler et al., 2002). In addition, experimental data showing stimulatory effect of genistein on proliferation of some breast cancer cells lines raise the problem of safety of genistein supplementation in women with diagnosed breast cancer (Lavigne et al., 2008).

Despite the controversies about safety and benefits of soy food supplementation, the pleiotropic activity of genistein, resulting from its interaction with numerous molecular targets, along with the possibility of chemical derivatization of a molecule place genistein among leading compounds for drug development.

This chapter deals with two main issues: (1) describes the main molecular targets affected by genistein and indicates alterations in signaling pathways, revealed by global gene profiling analyses, and (2) delineates the relevant examples of genistein derivatives synthesized with aim to obtain compounds exhibiting improved pharmacological activity, increased affinity

to molecular targets or altered mode of action as compared to the parent drug. The clinical utility of genistein-based pharmaceuticals is also discussed.

2. Molecular targets affected by genistein

Genistein is known for its pleiotropic effects, mediated by alteration of the activity of key enzymes involved in cell signaling, and by changes of the expression of the genes involved in various physiological processes. To the large group of genistein targets new proteins discovered with use of potent computational methods have joined recently. The interplay between different signaling pathways is extensively studied; however, exact molecular mechanisms have not been clearly defined yet.

2.1 Binding of genistein to different proteins

The proteins affected directly by genistein belong to many families. Among them are nuclear receptors, tyrosine-specific protein kinases, topoisomerases, ABC transporters and transport proteins present in the bloodstream (Tab. 1).

Nuclear receptors are members of a large family of transcription factors activated by binding of a ligand and regulating gene expression underlying a plethora of physiological and pathological states. Genistein binds to and activates estrogen receptors, peroxisome-proliferators activated receptors, liver X receptors and estrogen related receptors.

It was recognized very early that the chemical structure of genistein bears strong similarity to 17 β -estradiol, and that genistein binds to estrogen receptors (ER) and to sex hormone-binding globulins (Klinge, 2000; Kuiper et al., 1998; Kurzer, 2002). A functional interaction of genistein with estrogen receptors, leading to stimulation of ER responsive genes was confirmed in experiments in vitro (Birt et al., 2001; Kostelac et al., 2003). There are two isoforms of estrogen receptor, ER α and ER β , differentially expressed in tissues and exhibiting different biological functions. The hydrophobic ligand-binding cavity displays 53% of similarity between two isoforms (Manas et al., 2004). This pocket contains 12 α -helices and two β -sheets, connected by several short straight fragments. Inside a ligand binding cavity the ligand molecule is oriented with hydrogen bonding at the ends and hydrophobic van der Waals contacts along the body of the hormone. In the ER α functionally important polar amino acids in the binding pocket include: Glu-353, Arg-394, and His-524 (Tanenbaum et al., 1998). These aminoacids interact with 7 and 4' OH groups of genistein. Several other amino acid residues create hydrophobic bonds essential for stabilizing the nonpolar elements of the ligand ring structure. Genistein is regarded as an agonist of ER α . Although ligand binding domain sequence and structure in ER β is very similar to ER α and stabilization of a ligand occurs due to analogous hydrogen bonding with the side chains of Glu-305, Arg-346 and His-475 (Fig. 1), genistein binds to this form with higher affinity than to ER α (Manas et al., 2004). The position of the ligand in both receptor types is similar, but the volume of a cavity is smaller in ER β , and genistein is bound more tightly in the cavity. Despite the higher affinity to ER β than ER α , genistein is only partial agonist of ER β . The explanation may be derived from the different conformations of a ligand-bound state of ER α and ER β . Hormone-dependent activation of a receptor is a result of the movement of helix 12 from one position to another. The positional variability of this substructure appears to be a critical attribute of the ER receptors in their variable response to different ligands (Pike et al., 1999).

Recently it was shown that proteins constituting the family of estrogen related receptors (ERRs) are also able to bind genistein (Suetsugi et al., 2003). Although they display similarity to estrogen receptors, they do not bind estrogens. ERRs are referred to as orphan receptors, because no endogenous ligands required for their activity have been identified so far. The ligand-binding pockets of ERRs are very small (about half size of ER α) and partially filled with the aromatic bulky side chains of aminoacids forming the cavity, what is supposed to mimick the ligand-bound state inducing constitutive activity of the receptor. Surprisingly, genistein is a strong agonist of those receptors, augmenting their basal activity. Docking results showed that genistein, due to the small size of the cavity, is tightly packed and deeply docked into the ligand-binding site (Suetsugi et al., 2003) (Fig. 2).

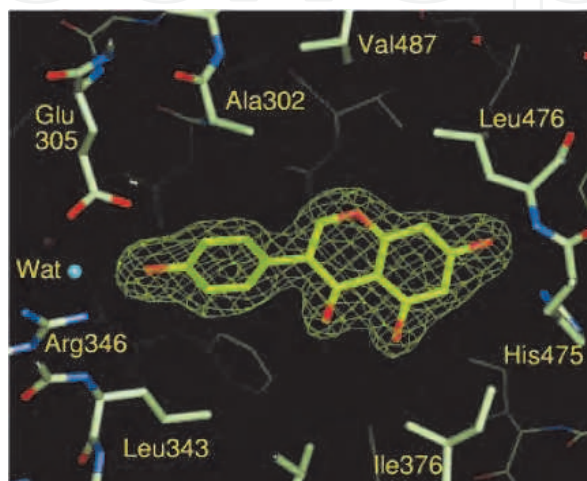


Fig. 1. The ligand-binding cavity in the genistein bound human estrogen receptor β . 4'OH group of genistein forms hydrogen bonds with the Glu-305, the Arg-346 and a water molecule; 7OH group forms hydrogen bond with His-475. Reprinted by permission from Macmillan Publishers Ltd: Pike et al. 1999, EMBO Journal Vol.18, No.17, 4608-4618, Copyright 1999.

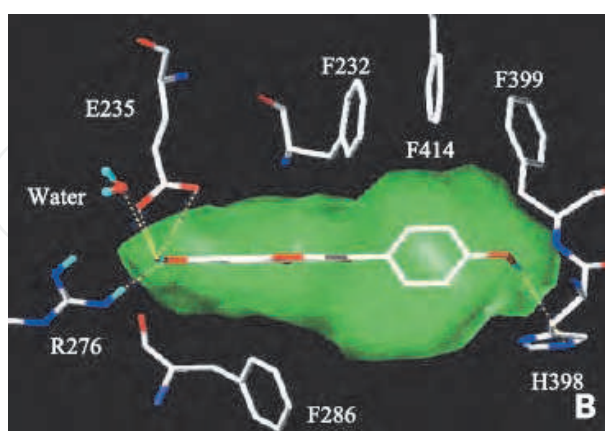


Fig. 2. The binding pocket of genistein-bound ERR α . 7OH group of genistein forms hydrogen bonds with the glutamate in helix 3, the arginine in helix 5, and a water molecule; 4'OH group forms hydrogen bond with H398. Adapted and reprinted by permission from American Association for Cancer Research, Suetsugi et al. 2003, Molecular Cancer Research Vol.1, No.13, 981-991.

Other members of nuclear receptor family activated by genistein are peroxisome proliferators-activated receptor γ (PPAR γ) (Dang et al., 2003) and PPAR α (Kim et al., 2004; Kim et al., 2005). The main role of PPAR γ is to control the genes involved in adipocyte differentiation and lipid storage. The structure of ligand binding domain in the PPAR γ is similar to both PPAR α and PPAR γ , and consists of 12 helices arranged in an antiparallel helix sandwich, and additional 3-stranded antiparallel β sheet (Cronet et al., 2001). Docking studies, supported by the functional assay, characterized genistein as a full PPAR γ agonist (Salam et al., 2008). Subsequent studies shown, that agonistic action of genistein on PPAR γ stimulates adipogenesis (Relic et al., 2009). It is worth to keep in mind that genistein concurrently activates two different transcriptional factors, ERs and PPAR γ , which have opposite effects on osteogenesis or adipogenesis. Thus, genistein as an agonist of both receptors may affect the balance between activated ERs and PPAR γ , which determines the final effects on osteogenesis and adipogenesis.

Very weak binding of genistein to androgen receptor (AR) was reported by Bectic et al. (2004). However, the inhibition of specific androgen binding was less than 25% at 1000-fold higher concentration of genistein (1 μ M) in a radioligand-binding assay. Moreover, this weak binding did not influenced AR transcriptional activity measured by a reporter gene assay in PC-3 and DU 145 cells. The authors concluded, that genistein influence the expression of AR dependent genes indirectly, by down-regulation of AR.

Another group of enzymes binding genistein are proteins, which share in their structure the consensus sequence for ATP binding, such as tyrosine kinesis, topoisomerases, ABC transporters, and ion channels. Although genistein does not resemble ATP, its binding is competitive to ATP.

Historically, the first proteins affected by genistein were protein tyrosine kinases (PTK) (Akiyama et al., 1987). Suppression of PTKs is thought to occur due to genistein binding with a common, highly conservative sequence at, or near to, the ATP-binding domain (Markovits et al., 1989; Akiyama et al., 1987). Genistein is a competitive inhibitor of ATP in a number of tyrosine kinases that utilize the G-X-G-X-X-G consensus for ATP binding (Akiyama et al., 1987).

To another group of proteins affected by genistein belong hexose transporters. The 12 transmembrane α -helical domains of the monomeric GLUT protein form a central water-filled pore, facilitating glucose transport. Vera et al. (1996) found that genistein inhibited transport of substrates by the GLUT1, blocking its ATP-binding domains. Similar mechanism of glucose uptake inhibition by genistein occurs in GLUT4 (Bazuine et al., 2005). Exact binding mode of genistein in GLUT1 is not known. It is hypothesized, that genistein, binding to the cytoplasmic surface of GLUT1, uses the sequences of close homologies to the sequences in the ligand-binding cavity of estrogen receptors (Afzal et al., 2002) (Fig. 3). These domains are in close vicinity or partially overlap the ATP-binding sites, so binding of estrogen, tamoxifen and genistein may competitively inhibit ATP binding.

The inhibition of topoisomerases by genistein is thought to be mediated by its binding to N-terminal ATP-binding motif. Topoisomerase II maintains the integrity of the cleaved DNA by forming covalent bonds with each newly created 5'-phosphate termini of the cleaved DNA segment. This transfer of phosphodiester bonds from DNA to topoisomerase II is similar to the autophosphorylation reaction of tyrosine kinases, where the enzyme forms a bond between its tyrosine and the phosphate group of ATP. Eucaryotic topoisomerase II α has two consensus ATP-binding motifs. Only Walker A site (residues 161-166 in human topoisomerase II α) is utilized for ATP binding in the eukaryotic type II enzyme. The Walker B site (residues 472-477), located near the region of the enzyme, in close proximity to the site

of DNA cleavage and ligation, has no known function for topoisomerase activity, but its consensus sequence (G-X-G-X-X-G), is the same, as the ATP-binding consensus sequence in a number of tyrosine kinases (Markowitz et al., 1989). Probably, this non-functional consensus site, common with protein kinases is the sequence of topoisomerase II α , which binds genistein (Bandelet & Osheroff 2007).

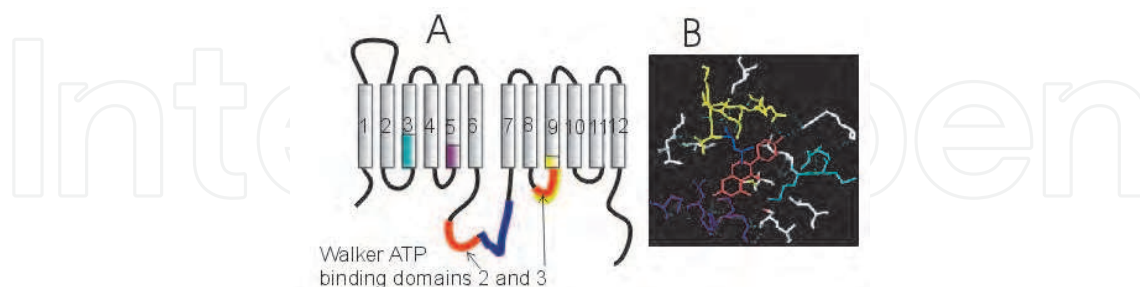


Fig. 3. Structure of GLUT1. A. Two-dimensional model of GLUT1 with Walker ATP-binding domains (red), and homologies to ER β (turquoise, violet, blue and yellow). B. Close view of H bonding interactions of genistein (dark red) with His and Arg of GLUT1. Colours on A and B match each other. Reproduced with permission, from Afzal et al. 2002, *Biochemical Journal* Vol. 365, No.3, 1707-1719, © the Biochemical Society.

Cystic fibrosis transmembrane conductance regulator (CFTR) belongs to ABC transporter-class ion channels, and transports chloride through epithelial cells membranes. Potentiation of Cl⁻ ion efflux through CFTR by genistein is thought to result from interaction of the isoflavonoid with one of two ATP-binding sites in the regulatory nucleotide-binding domains (NBD) of a protein. In CFTR, the membrane spanning domains form a pathway for passive anion flow that is gated by cycles of ATP binding and hydrolysis (Hwang & Sheppard 2009) (Fig. 4). It is established that ATP hydrolysis at ATP-binding site 2 is responsible for a rapid closure of the gate opened by ATP (Chen & Hwang, 2008; Gadsby et al., 2006). Competitive binding of genistein to the second ATP-binding site disables channel gating (Wang et al., 1998), what means that potentiation of CFTR Cl⁻ current is a result of the channel locking by genistein in a stable open state. Exact mode of genistein binding to CFTR is unknown, however docking studies indicate several putative binding sites in the protein (Huang et al, 2009) (Fig. 4B).

The next group of proteins binding genistein are blood proteins. Binding of genistein to human sex hormone-binding proteins (hSHBG) is reversible and competitive for both [3H]testosterone and [3H]17 β -estradiol (Dechaud et al., 1999). Genistein binding to hSHBG may influence its bioavailability to cell tissues, and displace endogenous sex steroid hormones from hSHBG binding sites.

Human serum albumin (HSA) with high affinity binding sites is a major transporter for delivering several endogenous compounds and drugs *in vivo*. Structural analysis showed that genistein binds to HSA *via* polypeptide polar groups (Mandeville et al., 2009). Binding of genistein to albumins is reversible, rapid and the concentration of unbound isoflavone is in an equilibrium state.

It is worth to note, that hemoglobin is able to bind genistein, what makes this most abundant protein of blood, important for genistein transportation, distribution and storage (Yuan et al., 2008).

Transthyretin (TTR) is a tetrameric β -sheet-rich transporter protein involved to some extent in the transport of thyroid hormone, thyroxine. TTR binds genistein via the thyroxine (T4)

binding sites. TTR has two identical funnel-shaped thyroxine-binding sites located at the dimer-dimer interface (Fig. 5). Binding of thyroxine stabilizes native, tetrameric state, whereas dissociation of the hormone promotes dissociation of the protein to monomers, and their abnormal aggregation, observed in human amyloid diseases. Since only 1% of TTR is bound to thyroxine, small molecules, such as genistein may help to stabilize the tetrameric structure. Genistein is known to potently inhibit TTR amyloid fibril formation (Green et al., 2005). In TTR, the mode of genistein binding is sequential, with negative cooperativity observed. Binding of the first genistein molecule to TTR generates allosteric adjustment of conformation in the second genistein binding site. The most stable conformation of TTR protein is observed when two molecules of genistein are bound to the tetramer (Trivella et al., 2010).

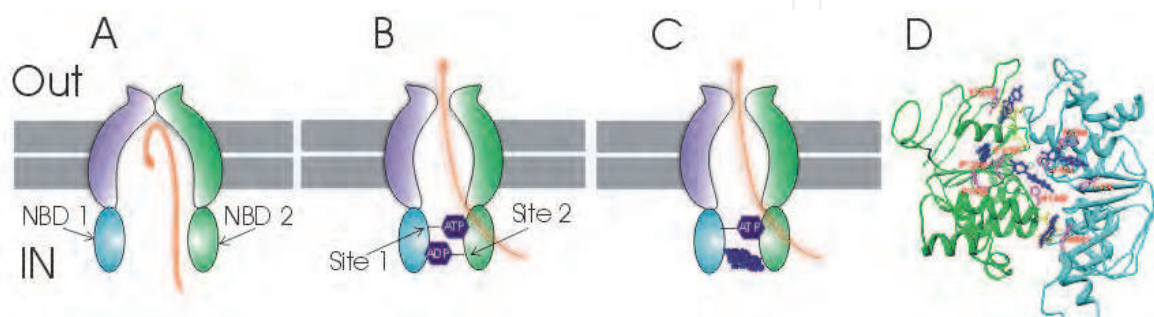


Fig. 4. The simplified model of CFTR Cl⁻ channel opening. A. closed state, B. open state, C. stable open state, forced by genistein (dark blue molecule), which blocks ATP-binding site 2. IN and OUT denote the intra- and extracellular sides of the membrane, respectively. NBD1 – turquoise, NBD2 – green, site 1 and site 2 – ATP-binding sites. D. A stereo view of five putative binding sites of genistein to human CFTR. Ball-and-stick molecules of genistein are shown in blue, and the ATP in yellow. Residues important for interacting with genistein are in magenta. A and B - Reproduced with permission from John Wiley and Sons, Hwang & Sheppard 2009, *Journal of Physiology*, Vol.587, No.10, 2151–2161, D - Reprinted from *Journal of Molecular Graphics and Modelling*, Vol.27, No. 7, Huang et al. 2009, Pages 822–828, Copyright (2009), with permission from Elsevier.

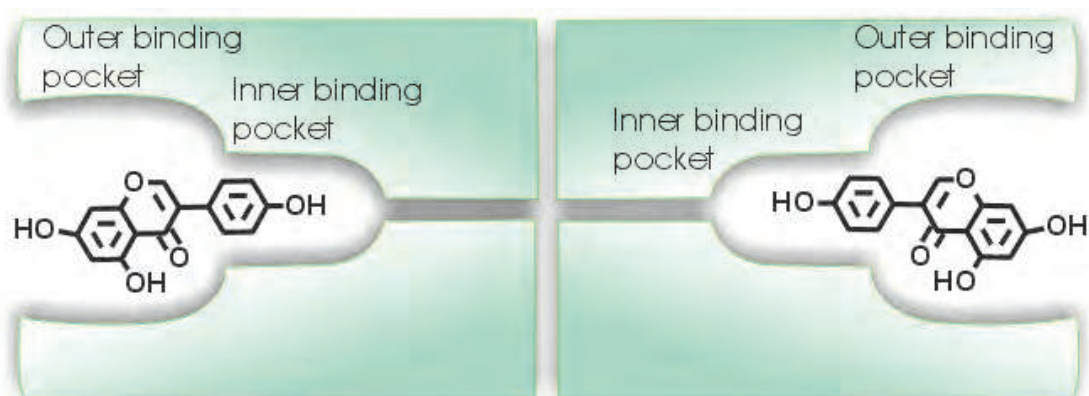


Fig. 5. Structure of transthyretin. A. Schematic representation of the tetrameric structure of TTR depicting the two thyroxine-binding sites with two molecules of genistein stabilizing the tetramer. Modified from Green et al., 2005, with permission. Copyright (2005) National Academy of Sciences, U.S.A.

There are also many intracellular proteins which functions are affected upon genistein binding listed in the Tab. 1., which does not fit any group described above, such as ornithine decarboxylase, aromatase CYP19 or tubulin. Cytoskeleton protein, tubulin binds genistein at ANS-binding site, what leads to depolymerization of microtubules (Mukherjee et al., 2010).

Classes of proteins binding genistein	Proteins	Type of influence on a protein activity	Binding affinity (Ki) or 50 % inhibitory concentration (IC50)	Source
Estrogen receptors	Er α	Agonist	Ki=370 nM IC ₅₀ =1.97-14 μ M	Matsuda et al., 2001, Güngör et al., 2006, Kostelac et al., 2003
	ER β	Partial agonist	Ki=24nM; IC ₅₀ =1.3-395 nM	Pike et al., 1999, Matsuda et al., 2001, Chesworth et al., 2005; Mewshaw et al., 2007
Estrogen related receptors	ERR α	Agonist	IC ₅₀ =2.4 μ M	Suetsugi et al., 2003
	ERR β	Agonist	IC ₅₀ >10 μ M	Suetsugi et al., 2003
	ERR γ	Agonist	IC ₅₀ >10 μ M	Suetsugi et al., 2003
Peroxisome proliferator activator receptor	PPAR γ	Agonist	Ki=5.7 μ M IC ₅₀ =16.7 μ M	Dang et al., 2003, Salam et al., 2008
Androgen receptor	AR	No transcription activation	Ki>>1 μ M	Bektic et al., 2004
Liver X receptor	LXR- α	Agonist	IC ₅₀ =31 μ M	Dodo et al., 2008
	LXR- β	Agonist	IC ₅₀ =22 μ M	Dodo et al., 2008
Tyrosine kinases	EGFR	Inhibitor	IC ₅₀ =22 μ M	Akiyama et al., 1987
	Pp60 v-src	Inhibitor	IC ₅₀ =26 μ M	Akiyama et al., 1987
	Pp110 gag-fes	Inhibitor	IC ₅₀ =24 μ M	Akiyama et al., 1987
	MEK4	Inhibitor	IC ₅₀ =0.4 μ M	Xu et al., 2009
	ABL	Inhibitor	IC ₅₀ =10 μ M	Traxler et al., 1995
	Protein kinase C	Inhibitor	IC ₅₀ =15 μ M	Traxler et al., 1995
	Tyrosine Kinase Syk	Inhibitor	IC ₅₀ =39 μ M	Xie et al, 2009
FGF receptor 1	FGF1	Inhibitor	IC ₅₀ <25 μ M	Rao, 1997
Ion channels	CFTR	Potentiator	Ki=1.8 μ M	Melani et al., 2010

Classess of proteins binding genistein	Proteins	Type of influence on a protein activity	Binding affinity (Ki) or 50 % inhibitory concentration (IC50)	Source
Glucose transporters	GLUT1	Inhibitor	Ki=4-12 μ M	Afzal et al., 2002; Vera et al. 1996
	GLUT4	Inhibitor	IC ₅₀ =20 μ M	Bazuine et al., 2005
MDR proteins	ABC G2	Substrate	n.a.	Imai et al., 2004; Zhang et al., 2004; Perez et al., 2009
Topoisomerase I	Topo I	Inhibitor	n.a.	Okura et al., 1988
Topoisomerase II	Topo II α	Inhibitor	IC ₅₀ <30 μ M	Bandeled & Osherooff, 2007
	Topo II β	Inhibitor	IC ₅₀ =30 μ M	Constantinou et al., 1995; Okura et al., 1988; Markovitz et al., 1989
	Bacterial gyrase	Inhibitor	IC ₅₀ >200 μ M	Bernard et al., 1997
	Bacterial topo IV	Inhibitor	IC ₅₀ =93 μ M	Bernard et al., 1997
Adenosine receptors	A1	Inhibitor	IC ₅₀ =2.6 μ M	Schulte & Fredholm, 2002
	A2A	Inhibitor	IC ₅₀ =15.3 μ M	Schulte & Fredholm, 2002
Aromatase	Cyp 19	Inhibitor	Ki=100 μ M	Paoletta et al., 2008
Tubulin	Tubulin	Polymerization inhibitor	Ki=20 μ M IC ₅₀ >87 μ M	Mukherjee et al., 2010
Ornithine decarboxylase	ODC	Inhibitor	>10 μ M	Fang & Cassida, 1999
Sex hormone-binding globulin	hSHBG	Competitive binding to testosterone and estradiol	Ka=1.7x10 ⁵ M ⁻¹ (Testosterone) Ka=6.3 x10 ⁵ M ⁻¹ (estradiol)	Dechaud et al.,1999
Albumins	HAS		K=2.4x10 ⁴ M ⁻¹	Mandeville et al., 2009 ; Bian et al. 2004
Haemoglobin			n.a.	Yuan et al., 2008
Transthyretin	TTR	Competitor of T4	Ki=70nM	Radovic et al., 2006
		Stabilisator of a tetramer	K _{d1} =40 nM, K _{d2} =1.4 μ M	Green et al., 2005

Table 1. Proteins binding genistein and the type of influence on their activity

New efficient computer-assisted methods facilitate rapid identification of protein targets of potential drugs (Chen et al., 2003). INVDOCK is one of *in silico* techniques specifically applied to identification targets of medicinal plants ingredients and synthetic chemicals. It is based on ligand-protein inverse docking of a tested ligand to known ligand-binding pockets of the proteins from a 3D structural database. Many proteins indicated by the aid of INVDOCK as potential targets of genistein were previously confirmed or implicated by experiments. This approach allowed also indication of multiple new targets with therapeutic implications, able to bind genistein. Among them are: thymidylate synthetase, purine nucleoside phosphorylase, cyclophilin A, farnesyltransferase, guanylyl cyclase, carbonic anhydrase (cancer treatment), DNA polymerase, (cancer and Herpes viral infection), inosine dehydrogenase, purine nucleoside phosphorylase (Malaria), dihydrofolate reductase (leprosy), phospholipase A2 (inflammation), carbonic anhydrase I (hypertension and glaucoma), protein kinase C (cardiovascular disease).

From many studies on the oral bioavailability of genistein it is clear that *in vivo* plasma concentrations of genistein is 0.1–8 μM at a dose of 16 mg/kg of body weight (Bloedon et al., 2002; Setchell et al., 2001). Tab. 1. shows that the concentration of genistein, inhibiting or stimulating several potential targets, is much higher than its concentration in plasma, thus its physiological relevance is disputable. However, it might be possible, that under chronic exposure, even weak effects of genistein on molecular targets influence the overall physiological status.

2.2 Signalling pathways influenced by genistein in microarrays profiling

Specific changes in gene expression profiles brought about by the genistein treatment can occur either due to direct influence of the flavonoid on activity of transcription factors or to indirect compensatory homeostatic mechanisms. A global analysis of gene expression in response to a pleiotropic compound, such as genistein, in models of different organs under physiologic and disease conditions appears to be essential for understanding the molecular mechanisms of genistein action and seems to be advantageous approach in comparison to “gene-by-gene” studies. In this chapter we summarize the most important observations derived from transcriptomic, microarray-based studies aimed to identify gene sets influenced by genistein in normal and tumor tissues.

In general, microarray data published so far supports existing hypotheses on the mechanisms of action of genistein, both beneficial for human health (i.e. reduction of cancer risk, amelioration of postmenopausal syndrome and decrease of bone resorption in postmenopausal women, lipid metabolism, cardiovascular homeostasis) (Kim et al., 2005; Lee et al., 2007; Pie et al., 2006; Rice et al., 2007) and unfavorable (as estrogen-dependent cancer cell proliferation and adverse effects on the reproductive organs or involution of thymus and auto-immune disorders) (Lee et al., 2007; Naciff et al., 2002; Selvaraj et al., 2005). Those homeostasis-maintaining or homeostasis-affecting effects are often observed at low concentrations of genistein, essentially not exceeding 5 μM .

Functional categorization of genes affected by genistein on transcriptional level repeatedly indicates genes involved in cell growth, cell cycle, apoptosis, cell signals transduction, angiogenesis, tumor cell invasion and metastasis, cholesterol synthesis and lipid metabolism (Kim et al. 2005; Li et al., 2004; Li & Sarkar, 2002; Niculescu et al., 2007; Pie et al., 2006; Rice et al., 2007; Selvaraj et al., 2005). Among the genes regulated by genistein is a group of genes with common mechanism of regulation by nuclear receptors: estrogen receptors (Selvaraj et al., 2005) and androgen receptor (Rice et al., 2007).

The papers comparing the expression profiles of cells treated with estradiol and genistein show a considerable overlap in the genes not only in reproductive organs, but also in other tissues influenced by estrogens. Among non-reproductive organs in which strong changes of expression profile occurred in estrogen receptor-dependent manner after treatment with genistein are bones (Pie et al., 2006), liver and adipose tissue (Kim et al., 2005), thymus (Selvaraj et al., 2005), lymphocytes (Niculescu et al., 2007), brain (Lyou et al., 2002), endothelial cells (Rimbach et al., 2008), cardiovascular system and muscles (Velders et al., 2010). It has to be noted that the expression profile influenced by high genistein uptake may not depend on genistein directly, but on the ability of individuals to metabolize genistein to equol (Niculescu et al., 2007).

The findings that dietary isoflavones may play a beneficial role in lipid and carbohydrate metabolism prompted the group of Kim et al. (2005) to perform cDNA microarray-based analysis in mice fed with high-fat diet (HFD) and supplemented with genistein. Mice fed the high-fat diet had abnormal lipid profiles, significantly greater body weight, and visceral fat accumulation and all these effects had been significantly reduced by genistein supplementation. Of much importance was also the observation that the expression of 84 genes affected by the high fat diet was normalized by genistein. The expression of genes encoding enzymes of cholesterol biosynthesis, which decreased by at least 50% in the high fat diet fed mice, returned to normal level as a result of genistein supplementation.

Pie et al. (2006) in their cDNA microarray study shown changes in the expression levels of bone metabolism-related genes, including those encoding calcitropic receptor, cytokines, growth factors and bone matrix proteins by genistein in ovariectomized mice. The study demonstrated that genistein prevented bone loss caused by estrogen deficiency without substantially affecting the uterus.

Many studies have correlated the soy-rich diet with a decreased risk of developing hormone-dependent cancers, including breast and prostate cancer. The result of a study carried on HCC1395 cells line derived from an early-stage primary breast cancer showed that genistein dose-dependently decreased cell viability and inhibited the invasion potential (Lee et al., 2007). The gene expression profile revealed upregulation of some genes which inhibit invasion and metastasis and downregulation of genes promoting these processes, indicating that genistein-induced alternations of gene expression involving metastasis may be exploited for setting up chemopreventive and therapeutic strategies, particularly for early-stage breast cancer.

The oligo-microarray study by Lavigne et al. (2008) performed on MCF-F breast cancer cells shown that at physiologic concentration (1 or 5 μM) genistein elicited an expression pattern suggestive of increased mitogenic activity, and at pharmacological level (25 μM) it induced a pattern that likely contributes to increased apoptosis, decreased proliferation and decreased total cell number. These results strength former observations of biphasic response of certain cell lines to genistein.

Genistein is also a candidate prostate cancer preventive phytochemical. DNA microarray approach to examine the effects of genistein at concentrations within its physiologic range on global gene expression patterns in androgen-responsive cancer cells shown a concentration-dependent modulation of multiple cellular pathways that are important in prostate carcinogenesis. Interestingly, the androgen receptor (AR)-mediated pathways, in particular, appeared to be modulated by genistein at low concentrations. The regulation of AR-mediated pathways is potentially the most relevant chemopreventive mechanism for genistein administered at physiologic levels (Rice et al., 2007; Takahashi et al., 2004).

Selvaraj et al. (2005) gained insight into signaling pathways that regulate various stages of thymocyte maturation, dependent on estradiol and genistein, and found that the effects of both compounds were similar, although, genistein down regulated more genes than estradiol. Genistein was also shown to induce genes involved in apoptosis, which is a continuous process in the thymus undergoing active thymocyte selection, but at the same time it affected genes which may facilitate thymic release of autoimmune cells.

Microarrays were also used to get closer insight into the influence of genistein on female reproductive organs. The study performed by Naciff et al. (2002) revealed that prenatal exposure to genistein altered the fetal gene-expression pattern of the rat uterus and ovaries in a similar manner as exposition to the estrogenic compounds, such as 17-ethynylestradiol and bisphenol A. Toxicogenomic analysis with use of cDNA microarray applied to determination of testicular mRNA profiles was proposed as a useful tool for evaluation of delayed long-term effects after fetal or neonatal exposure of mice to genistein (Adachi et al., 2004). Although no morphological changes in the testes of genistein-treated mouse were observed, the authors indicated the gene (GeneBank accession No. W49392), which might be useful biological marker, in addition to ER α and AR, for predicting the effects of neonatal exposure to genistein or related compounds.

The long lasting effects of genistein may result from epigenetic influence of genistein on gene expression. The use of differential methylation hybridization (DMH) arrays for screening of the changes in the methylation status of the cytosine guanine dinucleotide (CpG) islands in the mouse genome shown important genistein-induced alterations (Day et al., 2002). The study shown that changes in the methylation pattern reflected potential of genistein for preventing the development of certain prostate and mammary cancers by maintaining a protective DNA methylation profile (Day et al., 2002). The ability of genistein to change the methylation status was observed in several other studies. Genistein was shown to partially demethylate the promoter of the GSTP1 tumor suppressor gene in MDA-MB-468 breast cancer line (King-Batoon et al., 2008). Another study shown the change of methylation status in mice prenatally exposed to genistein (Vanhees et al., 2011). Genistein exposure was associated with hypermethylation of certain repetitive elements, what coincided with a significant down-regulation of estrogen-responsive genes and genes involved in hematopoiesis in bone marrow cells of genistein-exposed mice.

In contrast to studies aiming to establish the role of genistein in homeostasis, the experiments designed for identification of gene expression profiles associated with a therapy, are often carried with suprapharmacological concentrations of a drug. In several studies of this kind, the most of affected genes were not dependent on hormonal regulation (Farivar et al., 2003; Lavigne et al., 2008; Li & Sarkar, 2002). The genes repeatedly found to be down regulated by genistein, were those involved mainly in signal transduction, oncogenesis, cell proliferation, protein phosphorylation and transcription. On the other hand, genistein up-regulated genes were related mainly to signal transduction, protein dephosphorylation, heat shock response, inactivation of mitogen-activated protein kinase (MAPK), apoptosis and cell cycle arrest. Among the genes regulated by genistein there was a number of genes regulated by tyrosine kinases inhibitors, like Gleevec (STI-571), lavendustin and herbimycin (Farivar et al., 2003). Studies on the evaluation of the global transcript profile changes performed on different models could be a valuable approach to determine the similarity in the mode of action of genistein derivatives, comparing to a parent compound. This approach may be useful for description of potential "druggable" targets and determination the safety profile of new compounds.

3. Synthetic derivatives of genistein and their potential medicinal applications

Many opportunities for derivatization of genistein, apparent from its structural formula encourage the synthesis of derivatives with improved pharmacological profile. The chemical basis describing functionalization of three phenolic groups at C-5, C-7 and C-4' in typical *O*-acylation or *O*-alkylation reactions and skeletal modifications of genistein core, involving C-C bond formation is reviewed elsewhere (Rusin et al., 2010). Multiple examples of promising candidates intended to be used in therapy of different diseases are listed below. Among the diseases potentially treatable with the genistein derivatives are cancer, osteoporosis and metabolic disorders. Other suggested applications of genistein derivatives cover antibacterial and antiparasitic treatment. It must be noted, however, that most of presented derivatives have the status of experimental or investigational drugs.

3.1 Genistein derivatives for treatment of osteoporosis

Hormonal replacement therapy with synthetic estrogens was initially used for prevention of osteoporosis, however serious side effects of hormone replacement therapy stimulated the search for therapeutics, alternative to estrogens. Currently, among agents used in pharmacological prevention of osteoporosis are selective estrogen receptor modulators (SERMs), which function mainly as the antiresorptive agents (Reginster, 2011). Genistein, as a potential antiosteoporotic dietary supplement draw attention for many years, mostly on the basis of epidemiological observations (Knight & Eden, 1996; Messina, 1995). Moreover, genistein was reckoned as a safe supplement, because it did not produce the harmful, estrogen-like effects in the uterus. However, the overall conclusions of genistein supplementation and retardation of bone loss are ambiguous. The randomized, double-blind, and placebo-controlled study by Marini et al. (2007) in osteopenic postmenopausal women revealed decreased bone resorption and increased bone formation in the genistein group. However, the results of this study permit only the conclusion that genistein may prevent progress from the mild disease - osteopenia, to its severe form - osteoporosis. Thus, genistein can be effective rather in chemoprevention than treatment of this disease.

For a long period of time the synthetic isoflavone, ipriflavone (7-isopropoxyisoflavone) was an attractive candidate for a bone-building agent, due to its anabolic, but not estrogenic activity (Gennari, 1997). Ipriflavone inhibits bone resorption mediated by osteoclasts and stimulates activity of osteoblast in cell cultures and in experimental models of osteoporosis *in vivo*. However, clinical studies shown no statistically significant difference in annual percentage change from baseline lumbar spine and bone mineral density between those given ipriflavone and those given calcium (Alexandersen et al., 2001).

In the matter of fact, there is no universal drug for osteoporosis and new treatments, comprising of both new drugs and new drug combinations are still under clinical investigations. Side effects of currently used drugs, which are their obvious drawbacks, accounts for directing attention to phytoestrogens such as isoflavones and their derivatives as more reliable drugs.

Genistein modification aiming enhancement of its antiosteoporetic properties is presented by Wang *et al.* (2005), who synthesized a number of genistein derivatives in which the C-7 or C-4' hydroxyl groups were variously substituted. Among seventeen novel genistein derivatives the authors found five, which shown increased antiosteoporetic activity when compared to genistein, no acute toxicity and no stimulation of endometrium proliferation in

mouse model of osteoporosis. The derivatives inhibiting bone loss during estrogen shortage contained the 2-hydroxyethylthio motif, which the authors assumed to be a key pharmacophore. The best results were observed for 4',5,7-tri[3-(2-hydroxyethylthio)propoxy] isoflavone.

Useful information on the structural features of genistein derivatives related to antiosteoporotic effects may be drawn from the work of Zhang et al. (2008b). They discovered two natural derivatives of genistein in the stem bark of *Erythrina variegata* L.: 8-prenylgenistein and 6,8-diprenylgenistein stimulating osteoblastic proliferation, differentiation and mineralization in UMR 106 cells. These derivatives caused significant increase of alkaline phosphatase in cells treated by either 8-prenylgenistein or 6,8-diprenylgenistein for 48 h at the concentration of 10^{-10} M. A structure-activity relationship study indicates that prenylation at of genistein at C-8, but not at C-6, may increase its bone-protective effect.

Wang et al. (2007) presented the strategy, combining nitric oxide and genistein cooperation in inhibiting of a bone loss. The NO donor drugs effectively counteract bone mass loss occurring due to reduced rate of estrogen biosynthesis in postmenopausal women (Wimalawansa, 2000). What is particularly important, the NO donors not only slow down the rate of bone resorption, but also stimulate proliferation of osteoclasts (Hukkanen et al., 2003). In order to find a bifunctional derivative of genistein having both estrogenic properties and being an effective nitric oxide donor Wang et al. (2007) synthesized genistein 7,4'-(nitroxy) butyrate. Its NO-releasing capacity was studied *in vitro* using immature osteoblastic cell line MC3T3-E1 cells. It has been demonstrated that NO is released from the derivative less rapidly and for a longer time than from glyceryl trinitrate (GTN), the classical NO donor, routinely used in medical treatment (Wang et al., 2007). Using MTT assay and flow cytometry it was determined that the compound stimulated growth of MC3T3-E1 cells in a dose- and time-dependent manner, albeit the stimulation was weaker than that observed for an optimal concentration of estradiol. The measurements of the activity of a bone-specific isoform of alkaline phosphatase and the expression of osteocalcin, a specific marker for late osteoblast differentiation, as well as the rate of formation of calcific deposition revealed that the derivative stimulated osteoclast differentiation and mineralization more effectively than genistein, glyceryl trinitrate or combination of the two.

3.2 Genistein derivatives and hypertension

Genistein has been suggested to be protective in cardiovascular diseases. The study *in vivo* on spontaneously hypertensive rats had shown, that genistein reduced systolic blood pressure and enhanced endothelium-dependent aortic relaxation (Vera et al., 2007). Genistein reduced endothelial dysfunction due to increased endothelial nitric oxide synthase (eNOS) activity, associated with increased calmodulin-1 expression and decreased superoxide generation. Nitric oxide (NO) produced by eNOS is a well-known regulatory molecule involved in the modulation of contractility of vasculature thus maintaining vascular homeostasis (Miller & Megson, 2007).

Matsumoto et al. (2005) synthesized bifunctional derivative of genistein, which was aimed to inhibit tyrosine kinases, implicated in development of a hypertension, and release nitrogen oxide to enhance the effect. The authors synthesized two novel genistein derivatives 7-[(4-nitroxy)butyroyl]-genistein and 7-[(4nitrooxymethyl)-(alpha-methyl)phenylpropanyl]-genistein, and assessed their ability to relax rat endothelium-

denuded aortic strips. Both derivatives and genistein itself induced aortic relaxation in the following order: 7-[(4nitrooxymethyl)-(alfa-methyl)phenylpropanoyl]-genistein > 7-[(4-nitroxy)butyroyl]-genistein > genistein. The relaxation induced by the tested genistein derivatives was abolished by a guanylyl cyclase inhibitor, which proved, that genistein derivatives indeed acted as NO donors.

3.3 Genistein and its derivatives for treatment of cystic fibrosis

Genistein was shown to partially activate the defective chloride channels (cystic fibrosis transmembrane regulator, CFTR) associated with cystic fibrosis (CF). Genistein not only partially restored the CFTR activity but also augmented CFTR maturation and increased its localization at the cell surface (reviewed by Węgrzyn et al., 2010). Pre-clinical studies with genistein have provided a basis for clinical trials with CF patients, and a Phase II clinical study is currently underway. So far, genistein derivatives for potential treatment of cystic fibrosis have not been studied extensively. Galiotta et al. (2001) generated a combinatorial compound library based on two lead compounds, flavones and benzo[c]quinoliziniums, which activate CFTR Cl²⁻ conductance by direct interaction with the CFTR molecule. Among several novel derivatives they identified compounds with high potency to activate CFTR, 7,8-benzoflavones, containing features of both flavones and benzo[c]-quinoliziniums.

3.4 Derivatives with antimicrobial and antiparasitic activity

Antimicrobial properties of genistein are described in many papers, although the exact mechanism of this activity remains largely unknown (Hong et al., 2006; Ulanowska et al., 2006; Verdrengh et al., 2004). Cell survival studies suggest that genistein is a bacteriostatic, rather than a bactericidal agent (Ulanowska et al., 2007). There is a suggestion that antibacterial properties of genistein may be mediated by the stabilization of the covalent topoisomerase II-DNA cleavage complex (Verdrengh et al., 2004). The concentration of genistein necessary for bacterial growth retardation depends on the strain, but is regarded as relatively high (100 μM).

Zhang et al. (2008a) reported the derivatization of genistein leading to an increased antibacterial and antifungal activity. They prepared three series of derivatives in which the genistein ring system was linked to the heterocyclic moieties with 2-carbon, 3-carbon or 4-carbon spacers. Among these compounds, five exhibited good antibacterial activities, while one of them also showed notable antifungal activity. The activity of the mentioned derivatives was several fold higher than that of genistein.

The antimicrobial activity of genistein derivatives was also described by Li et al. (2008). They synthesized and tested 14 new deoxybenzoin derivatives of genistein and found that dimeric forms were generally more active than genistein or deoxybenzoin against selected microorganisms.

Several genistein derivatives are indicated for treatment of parasitic diseases. The potential use of genistein derivatives for anti-protozoan therapies were reported by Gargala et al. (2005) and Stachulsky et al. (2006), and, for anti-helminthic treatment by Naguleswaran et al. (2006). Gargala et al. (2005) screened fifty-two dihydroxyisoflavone and trihydroxydeoxybenzoin derivatives for their influence on protozoan parasites life cycle: *Neospora caninum*, *Sarcocystis neurona* and *Cryptosporidium parvum*. Two agents selected in this screening: 3'-bromo and 4'-bromo genistein were tested as in *Cryptosporidium parvum*-

infected immunosuppressed gerbils. It was found, that these compounds more effectively abolished fecal microscopic oocyst shedding than two routinely used drugs, nitazoxanide and paromomycin.

Some of genistein derivatives described previously by Gargala (2005) were tested for inhibitory effects on the larval development of tapeworms *Echinococcus sp.* (Naguleswaran et al., 2006). The study shown, that 2'-bromo- and 6'-bromo genistein induced considerable damage in *E. granulosus* protoscolex. The above mentioned genistein derivatives are safe in terms of side effects caused by the estrogen receptor stimulation, because they do not bind to ER. These derivatives were shown to be selective for parasites, without antibacterial activity (Stachulsky et al., 2006), what allows to avoid the development of resistant bacterial strains.

3.5 Derivatives of genistein designed for anti-cancer therapy

Several strategies of genistein modification were applied in order to put its anticancer potential in use. Among them are targeted therapy and chemical modification of a molecule, so that to improve the interaction with molecular targets. Examples of those modifications are described below.

3.5.1 Targeting genistein to cancer cells by conjugation with antibodies or peptide ligands

Major strategy of targeted therapy is to construct two-domain drugs, in which one domain recognizes the target cells, whereas the other one exerts a therapeutic activity. In order to selectively target genistein to intra-cellular kinase domain of epidermal growth factor receptor (EGFR) Uckun et al. (1998) obtained a conjugate of genistein with epidermal growth factor (EGF) via photochemical cross-linking. This conjugate was intended to target cancer cells overexpressing the epidermal growth factor receptor (EGFR). It was expected, that internalization of the conjugate should increase the intracellular concentration of genistein, and lead to efficient inhibition of the EGFR tyrosine kinase activity. In vitro studies confirmed strong proapoptotic activity of a conjugate in human breast cancer cells. (Uckun et al., 1998). Moreover SCID mice bearing tumors of human breast cancer cells (MDA-MB-231), treated intraperitoneally with the conjugate at 100 ug/day for 10 days showed significantly better survival as compared to mice treated with adriamycin, cyclophosphamide or methotrexate (Uckun et al., 1998).

A similar genistein targeting strategy, based on expected local increase of genistein concentration, was used for experimental treatment of leukemias (Ek et al., 1998). Genistein was conjugated to B43 antibody, recognizing the CD19 antigen, present on the surface of B lymphocytes and absent from plasma cells. CD19 is an adaptor protein for Lyn tyrosine kinase, amplifying signals transduction from nonreceptor Src tyrosine kinases. The study was performed on SCID mice bearing human acute lymphoblastic leukemia (ALL) or non-Hodkin's lymphoma shown the conjugate to be more therapeutically effective than cytostatics routinely used for treatment of this kind of leukemias (Ek et al., 1998). In subsequent *in vivo* study performed on cynomolgus monkeys the conjugate administered intravenously shown no toxicity during long term observation (Messinger et al., 1998). These highly encouraging results inclined the authors to perform phase I clinical study (Uckun et al. 1999). The pilot study of B43-genistein in 15 patients with refractory B-lineage acute lymphoblastic leukemia shown that the conjugate was well tolerated by all patients with no life-threatening side effects. There was one durable complete remission and two transient responses.

More recently, Gentile et al. (2003) used genistein-monoclonal antibody approach to treat SW-620 and HT-29 colon cancer cells. The conjugate of genistein and 17.1A monoclonal antibody recognizing an epithelial membrane antigen expressed in colon cancer significantly inhibited cell growth *in vitro* and *in vivo*, and induced apoptosis.

3.5.2 Genistein as a vector selectively targeting cytostatic drugs to ER positive cancers

Interesting therapeutic approach is the use of genistein as a carrier, delivering drugs to cells expressing target recognized by this isoflavonoid. However, some difficulties must be overcome: (1) cytotoxic agent in a conjugate must not produce a loss of genistein binding to the target protein, (2) the target of a cytotoxic agent should be present in the subcellular structure which is likely to be achievable by a carrier, (3) the concentration of the receptor should be high, and its expression should not be down-regulated by a carrier.

An example of the above mentioned strategy was the use of genistein derivative, 6-carboxymethylgenistein (6CG) as a potential vector of a cytostatic drug, daunomycin to estrogen receptor expressing cells (Somjen et al., 2002; Somjen et al., 2003). Although the relative binding affinity of 6-CG was 0.1% to ER β and 0.01% to ER α , respectively as compared to the estradiol, it was shown that 6-CG activated the receptor, which translocated to the nucleus. Transactivation studies proved that 6-CG is a ligand of ERs. In the absence of estradiol 6-CG was found to be an agonist, while in the presence of estradiol it shown moderate antagonist activity for ER α (Somjen et al., 2003). The cytotoxicity of this conjugate was tested against H295R cells. At low daunomycin concentration (0.3-3nM) the cytotoxicity of a conjugate was 10 times higher than that of free drug, what indicated successful targeting of a conjugate. At higher concentration (30nM) the differences were less profound, and no differences were observed between daunomycin and its conjugate with 6-CG, what indicates that the toxicity was a result of non-specific, high intracellular concentration of daunomycin. The targeting of daunomycin conjugated to 6-CG via ER was also confirmed by the experiment with cells devoid of ER, where no differences in toxicity of a conjugate and free daunomycin were observed (Somjen et al., 2003).

3.5.3 Genistein derivatives designed for treatment of hormone dependent cancers

Endocrine treatment with selective estrogen-receptor modulators (SERMs), such as tamoxifen and raloxifene is of major therapeutic value in patients with estrogen-receptor positive tumors. Hormone-dependent breast cancer tumors contain estrogen receptors and tumor growth depends on estrogens. Tamoxifen, a partial nonsteroidal estrogen agonist, is a competitive inhibitor of estradiol, and the prototype of SERMs. However, after long exposure to the tamoxifen the resistance often develops, so designing and synthesis of new antiestrogens for treatment of breast cancer is of much importance.

Very promising trisubstituted derivatives of genistein able to bind estrogen receptor with low affinity were recently described by Davis et al. (2008). Several compounds were able to inhibit cell proliferation in a dose-dependent manner, and compounds containing the bulky 7-phenylmethoxy substituent were toxic for both hormone-dependant MCF-7 cells and hormone-independent MDA-MB-231 cells. Thus, the synthetic tri-substituted isoflavones act on multiple signaling pathways leading to activation of mechanisms of cell-death and ultimately affecting survival of breast cancer cells. A novel genistein derivative exhibiting significantly higher antiproliferative activity than the parent drug was recently obtained by

Kohen et al., (2007) by attaching an *N*-tert-butoxycarbonylo-1,6-diamino-hexane group to C2 of genistein. Although this novel genistein derivative did not show estrogenic activity, its antiproliferative activity was different in estrogen-sensitive cancer cell lines expressing ER α and ER β mRNA at different ratios. The highest antiproliferative effect measured by radioactive thymidine incorporation was observed for an estrogen-sensitive colon cancer cell line (320DM), and the lowest for an ovarian cancer cell line (A2780). Interestingly, the genistein derivative was more toxic for cells that preferentially expressed mRNA for ER β , relative to ER α .

3.5.4 High-throughput screening of genistein derivatives

In recent years a search for anticancer cytostatics based on the synthesis of libraries of differently substituted derivatives of genistein, followed by high-throughput screening *in vitro* has been intensified. Although it looks, to some extent, like trusting in serendipity, it allows to empirically find the most promising drug candidates.

Such screening of more than 350 genistein analogues allowed to find several putative drugs for clinical development (Novogen). Among them was isoflaven phenoxodiol, which has been granted fast track status from the FDA to facilitate its development as a therapy for recurrent ovarian and prostate cancers (Silasi et al., 2009). Other compounds: triphendiol, NV-143 and NV-128, which are further derivatives of phenoxodiol, are still investigational drugs.

Phenoxodiol was intended for usage in a therapy of early-stage prostate cancer, late-stage, hormone-refractory prostate cancer, early stage cervical and vaginal cancer, chemo-resistant and chemo-refractory ovarian cancer. It was shown to induce death of cancer cells through pleiotropic mechanism: inhibition of the anti-apoptotic proteins FLIP and IAP and the increase of the pro-apoptotic protein BAX, inhibition of tyrosine kinases and topoisomerase II in a dose-dependent manner (Alvero et al., 2006; Kluger et al., 2007; Constantinou et al., 2002, Sapi et al., 2004]. Phenoxodiol was tested in phase 3 OVATURE trial in women with recurrent ovarian cancer. No statistically significant improvement in its primary (progression-free survival) or secondary (overall survival) endpoints were found, so the study was terminated (Howes et al., 2011).

Triphendiol is tested for use against pancreas and bile duct cancers and found to act synergistically with gemcitabine (Saif et al., 2009). NV-143 was found to be effective against multiple melanoma cell lines, while NV-128, demonstrated efficacy in monotherapy and as a chemosensitizer in non-small cell lung carcinoma (NSCLC) cell lines. Interestingly, NV-128 induced cell death *via* a caspase-independent pathway and autophagic cell death (Alvero et al., 2009). In summary, triphendiol, NV-143 and NV-128 exhibited a good safety profile, they were well tolerated and non-clastogenic. Effective inhibition of tumor proliferation was shown in animal models after oral administration of the tested drugs.

3.5.5 Synthetic glycoconjugates of genistein interacting with mitotic spindle

The effectiveness of microtubule-targeting drugs for the treatment of a broad range of human cancers has been shown in many clinical studies. The search for compounds with similar mechanisms of action to taxanes or vinca alkaloids resulted in the discovery of a number of novel microtubule-targeting drugs, the majority of which are natural products.

Although, genistein was recently shown to interact with interphase microtubules (Mukherjee et al., 2010), its clinical use as an antimetabolic drug is rather doubtful due to very high concentration necessary to achieve this effect. However, it seems that chemical

derivatization can help to obtain novel compounds exhibiting increased affinity to microtubules. We found, among the glycosidic derivatives described by Polkowski et al. (2004), that the compound named G21 (Fig. 6), which inhibited cell proliferation at the concentration 10 times lower than genistein, interacted with mitotic spindle (Rusin et al., 2009).

This compound caused remarkable mitotic block at the concentration inhibiting cell proliferation by half, compared to the control. Our observations were recently confirmed by others (Ahmed et al., 2011). Earlier studies shown that the structure of G21 molecule was stable, it did not hydrolyze under *in vitro* cell culture conditions (Ksycińska et al., 2004) and its toxicity against cancer cells was higher than against normal ones (Popiołkiewicz et al., 2005). The continuation of our work on glyconjugates of genistein exhibiting antimetabolic activity pointed another molecule, called Ram3 (Fig. 6), as a potent agent affecting mitotic spindle (Rusin et al., 2011) and leading to apoptotic cell death.

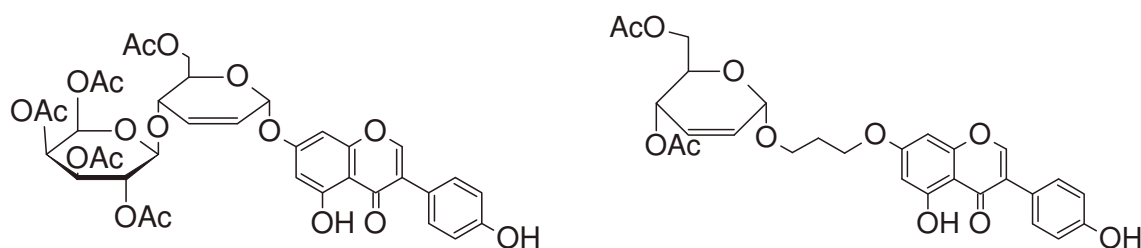


Fig. 6. Structure of genistein glycoconjugates showing antimetabolic activity. A. G21, B. Ram3.

4. Conclusion

Many studies concerning the biological properties of genistein analogues demonstrated that the modification of the parent isoflavone may lead to compounds exhibiting not only enhancement of the activities already known, but also revealed novel properties, not observed for the parent compound. The biological activity of the synthetic derivatives of genistein, briefly summarized in this review, indicate that, at least some of them can be viewed as important lead compounds for further modifications. Although most of the derivatives have the status of investigational or experimental drugs, multiple identified molecular targets of genistein identified so far give hope that clinically applicable and target-specific genistein derivatives may appear in the future.

There are obviously open questions, which diseases such genistein derivatives would be addressed for and whether they would be therapeutically useful in monotherapy or - what seems more probable - in combination therapies.

5. Acknowledgment

We would like to acknowledge our colleagues for working together on the glycoconjugates of genistein with antimetabolic properties, which is our small contribution into field of genistein derivatives for medicinal applications: Professor Grzegorz Gryniewicz and Professor Wiesław Szeja for all inspiring discussions and designing the glycoconjugates of genistein, Ms Jadwiga Zawisza for chemical syntheses and all colleagues who carried cytotoxicity assays, dr Magdalena Glowala-Kosinska, Dr Agnieszka Gogler, Ms Aleksandra Gruca and Ms Katarzyna Kujawa.

6. References

- Adachi, T.; Ono, Y.; Koh, K.B.; Takashima, K.; Tainaka, H.; Matsuno, Y.; Nakagawa, S.; Todaka, E.; Sakurai, K.; Fukata, H.; Iguchi, T.; Komiyama, M. & Mori, C. (2004). Long-term alteration of gene expression without morphological change in testis after neonatal exposure to genistein in mice: toxicogenomic analysis using cDNA microarray. *Food and Chemical Toxicology*, Vol.42, No.3, (March 2004), pp. 445-452, ISSN 0278-6915
- Afzal, I.; Cunningham, P. & Naftalin, R.J. (2002) Interactions of ATP, oestradiol, genistein and the anti-oestrogens, faslodex (ICI 182780) and tamoxifen, with the human erythrocyte glucose transporter, GLUT1. *Biochemical Journal*, Vol.365, No.3, (August 2002), pp. 1707-1719, ISSN 0264-6021
- Ahmed, A.A.; Goldsmith, J.; Fokt, I.; Le. X.F.; Krzysko, K.A.; Lesyng, B.; Bast, R.C. & Priebe, W. (2011). A genistein derivative, ITB-301, induces microtubule depolymerization and mitotic arrest in multidrug-resistant ovarian cancer. *Cancer Chemotherapy and Pharmacology* [Epub ahead of print] DOI: 10.1007/s00280-011-1575-2, ISSN 0344-5704
- Akiyama, T.; Ishida, J.; Nakagawa, S.; Ogawara, H.; Watanabe, S.; Itoh, N.; Shibuya, M. & Fukami, Y. (1987). Genistein, a specific inhibitor of tyrosine-specific protein kinases. *Journal of Biological Chemistry*, Vol. 262 No. 12, (April 1987) pp. 5592-5595, ISSN 0021-9258
- Alexandersen, P.; Toussaint, A.; Christiansen, C.; Devogelaer, J-P.; Roux, C.; Fechtenbaum, J.; Gennari, C. & Reginster, J.Y. (2001). Ipriflavone in the Treatment of Postmenopausal Osteoporosis. A Randomized Controlled Trial. *Journal of the American Medical Association*, Vol. 285, No.11, (March 2001), pp. 1482-1488, ISSN 00987484
- Alvero, A.B.; Montagna, M.K.; Chen, R.; Kim, K.H.; Kyungjin, K.; Visintin, I.; Fu, H.H.; Brown, D. & Mor, G. (2009). NV-128, a novel isoflavone derivative, induces caspase-independent cell death through the Akt/mammalian target of rapamycin pathway. *Cancer*. Vol. 115, No 14, (July 2009), pp. 3204-3216, ISSN 1097-0142
- Alvero, A.B.; O'Malley, D.; Brown, D.; Kelly, G.; Garg, M.; Chen, W.; Rutherford, T. & Mor, G. (2006). Molecular mechanism of phenoxodiol-induced apoptosis in ovarian carcinoma cells. *Cancer*, Vol. 106, No.3, (February 2006) pp. 599-608, ISSN 1097-0142
- Bandelet, O.J. & Osheroff, N. (2007). Bioflavonoids as poisons of human topoisomerase II alpha and II beta. *Biochemistry*. Vol. 46, No 20, (May 2007), pp. 6097-6108, ISSN 0006-2960
- Bazuine, M.; van den Broek, P.J.A. & Maassen, J.A. (2005). Genistein directly inhibits GLUT4-mediated glucose uptake in 3T3-L1 adipocytes. *Biochemical and Biophysical Research Communications* Vol. 326, No. 2, (January 2005), pp. 511-514, ISSN 0006-291X
- Bektic, J.; Berger, A.P.; Pfeil, K.; Dobler, G.; Bartsch, G. & Klocker, H. (2004). Androgen receptor regulation by physiological concentrations of the isoflavonoid genistein in androgen-dependent LNCaP cells is mediated by estrogen receptor beta. *European Urology* Vol.45, No.2, (February 2004), pp. 245-251, ISSN 0302-2838

- Bernard, F.X. ; Sable, S. ; Cameron, B. ; Provost, J.; Desnottes, J.F.; Crouzet, J. ; & Blanche, F. (1997). Glycosylated Flavones as Selective Inhibitors of Topoisomerase IV. *Antimicrobial Agents and Chemotherapy*, Vol.41, No.5, (May 1997), pp. 992-998, ISSN 0066-4804
- Bian, Q.; Liu, J.; Tian, J. & Hu, Z. (2004). Binding of genistein to human serum albumin demonstrated using tryptophan fluorescence quenching. *International Journal of Biological Macromolecules* Vol.34, No.5, (October 2004), pp. 333-337, ISSN 0141-8130
- Birt, D.F.; Hendrich, S. & Wang, W. (2001). Dietary agents in cancer prevention: flavonoids and isoflavonoids. *Pharmacology & therapeutics* Vol.90, No. 2-3, (March 2001), pp. 157-177, ISSN 0163-7258
- Bloedon, L.T.; Jeffcoat, A.R.; Lopaczynski, W.; Schell, M.J.; Black, T.M.; Dix, K.J.; Thomas, B.F.; Albright, C.; Busby, M.G.; Crowell, J.A. & Zeisel, S.H. (2002). Safety and pharmacokinetics of purified soy isoflavones: single-dose administration to postmenopausal women. *The American Journal of Clinical Nutrition*, Vol. 76, No. 5, (November 2002), pp. 1126-1137, ISSN 0002-9165
- Chen, T.Y. & Hwang, T.C. (2008). CLC-0 and CFTR: chloride channels evolved from transporters. *Physiological Review*, Vol.88, No.2, (April 2008), pp. 351-387, ISSN 0031-9333
- Chen, X.; Ung, C.Y. & Chen, Y. (2003). Can an in silico drug-target search method be used to probe potential mechanisms of medicinal plant ingredients? *Natural Product Reports* Vol.20, No.4, (August 2003), pp. 432-444, ISSN 0265-0568
- Chesworth, R; Wessel, M.D.; Heyden, L.; Mangano, F.M.; Zawistoski, M.; Gegnas, L.; Galluzzo, D.; Lefker, B.; Cameron, K.O.; Tickner, J.; Lu, B.; Castleberry, T.A.; Petersen, D.N.; Brault, A.; Perry, P.; Ng, O.; Owen, T.A.; Pan, L.; Ke, H.Z.; Brown, T.A.; Thompson, D.D. & DaSilva-Jardine, P. (2005). Estrogen receptor beta selective ligands: discovery and SAR of novel heterocyclic ligands. *Bioorganic & Medicinal Chemistry Letters*, Vol.15, No.24, (December 2005), pp. 5562-5566, ISSN 0960-894X
- Constantinou, A.; Mehta, C.; Runyan, K.R; Vaughan, A. & Moon, R. (1995). Flavonoids as DNA topoisomerase antagonists and poisons: structure-activity relationships. *Journal of Natural Products*, Vol.58, No.2, (February 1995), pp. 217-225, ISSN 0163-3864
- Constantinou, A.I. & Husband, A. (2002). Phenoxodiol (2H-1-benzopyran-7-0,1,3-(4-hydroxyphenyl)), a novel isoflavone derivative, inhibits DNA topoisomerase II by stabilizing the cleavable complex. *Anticancer Research*, Vol. 22, No.5, (September-October 2002), pp. 2581-2585, ISSN 0250-7005
- Cronet, P.; Petersen, J.F.W.; Folmer, R.; Blomberg, N.; Sjoblom, K.; Karlsson, U.; Lindstedt, E.L. & Bamberg, K. (2001). Structure of the PPAR α and - γ Ligand Binding Domain in Complex with AZ 242; Ligand Selectivity and Agonist Activation in the PPAR Family. *Structure*, Vol.9, No.8, (August 2001), pp. 699-706, ISSN 0910-8270
- Dang, Z.C.; Audinot, V.; Papapoulos, S.E.; Boutin, J.A. & Lowik, C.W.G.M. (2003). Peroxisome Proliferator-activated Receptor γ (PPAR γ) as a Molecular Target for the Soy Phytoestrogen Genistein. *Journal of Biological Chemistry*, Vol. 278, No.2, (January 2003), pp. 962-967, ISSN 0021-9258

- Davis, D.D.; Díaz-Cruz, E.S.; Landini, S.; Kim, Y.W. & Brueggemeier, R.W. (2008). Evaluation of synthetic isoflavones on cell proliferation; estrogen receptor binding affinity; and apoptosis in human breast cancer cells. *The Journal of Steroid Biochemistry and Molecular Biology*, Vol. 108, No.1-2, (January 2008), pp. 23-31, ISSN 0960-0760
- Day, J.K.; Bauer, A.M.; desBordes, C.; Zhuang, Y.; Kim, B.E.; Newton, L.G.; Nehra, V.; Forsee, K.M.; MacDonald, R.S.; Besch-Williford, C.; Huang, T.H.M. & Lubahn D.B. (2002). Genistein Alters Methylation Patterns in Mice. *Journal of Nutrition*, Vol.132, No.8, (August 2002), pp. 2419S-2423S, ISSN 0022-3166
- Dechaud, H.; Ravard, C.; Claustrat, F.; de la Perriere, A.B. & Pugeat, M. (1999). Xenoestrogen interaction with human sex hormone-binding globulin (hSHBG). *Steroids*, Vol.64, No.5, (May 1999), pp. 328-334, ISSN 0039-128X
- Dodo, K.; Aoyama, A.; Noguchi-Yachide, T.; Makishima, M.; Miyachi, H. & Hashimoto, Y. (2008). Co-existence of alpha-glucosidase-inhibitory and liver X receptor-regulatory activities and their separation by structural development. *Bioorganic & Medicinal Chemistry*, Vol.16, No.8, (April 2008), pp. 4272-4285, ISSN 0968-0896
- Ek, O.; Yanishevski, Y.; Zeren, T.; Waurzyniak, B.; Gunther, R.; Chelstrom, L.; Chandan-Langlie, M.; Schneider, E.; Myers, D.E.; Evans, W. & Uckun, F.M. (1998). In vivo toxicity and pharmacokinetic features of B43(Anti-CD19)-Genistein immunoconjugate. *Leukemia and Lymphoma*, Vol.30, No.3-4, (July 1998), pp. 389-394, ISSN 1042-8194
- Fang, N. & Casida, J.E. (1999). New bioactive flavonoids and stilbenes in cube resin insecticide. *Journal of Natural Products*, Vol.62, No.2, (February 1999), pp. 205-210, ISSN 0163-3864
- Farivar, R.S.; Gardner-Thorpe, J.; Ito, H.; Arshad, H.; Zinner, M.J.; Ashley, S.W. & Whang E.E.; (2003). The Efficacy of Tyrosine Kinase Inhibitors on Human Pancreatic Cancer Cell Lines. *Journal of Surgical Research*, Vol.115, No.2, (December 2003), pp. 219-225, ISSN: 0022-4804
- Gadsby, D.C.; Vergani, P. & Csanady, L. (2006). The ABC protein turned chloride channel whose failure causes cystic fibrosis. *Nature*, Vol.440, No.7083, (March 2006), pp. 477-483, ISSN 0028-0836
- Galiotta, L.J.V.; Springsteel, M.F.; Eda, M.; Niedzinski, E.J.; By K; Haddadin, M.J.; Kurth, M.J.; Nantz, M.H. & Verkman, A.S. (2001). Novel CFTR chloride channel activators identified by screening of combinatorial libraries based on flavone and benzoquinolizinium lead compounds. *The Journal of Biological Chemistry*, Vol.276, No.23, (June 2001), pp. 19723-19728, ISSN 0021-9258
- Gargala, G.; Baishanbo, A.; Favennec, L.; Francois, A.; Ballet, J.J. & Rossignol, J.F. (2005). Inhibitory activities of epidermal growth factor receptor tyrosine kinase-targeted dihydroxyisoflavone and trihydroxydeoxybenzoin derivatives on *Sarcocystis neurona*; *Neospora caninum*; and *Cryptosporidium parvum* development. *Antimicrobial Agents and Chemotherapy*, Vol.49, No.11, (November 2005), pp. 4628-4634, ISSN: 0066-4804
- Gennari, C. (1997). Ipriflavone: Background. *Calcified Tissue International*, Vol.61, No.1 Supplement, (1997) pp. S3-S4, ISSN 0171-967X

- Gentile, M.S.; Vasu, C.; Green, A.; Murillo, G.; Das Gupta, T.K.; Constantinou, A.I.; Prabhakar, B.S. & Salti G.I. (2003). Targeting colon cancer cells with genistein-17.1A immunoconjugate; *International Journal of Oncology*, Vol.22, No.5, (May 2003), pp. 955-959, ISSN 1019-6439
- Green, N.S.; Foss, T.R. & Kelly, J.W. (2005). Genistein; a natural product from soy; is a potent inhibitor of transthyretin amyloidosis. *Proceedings of the National Academy of Sciences* Vol.102, No.41, (October 2005), pp. 14545-14550, ISSN-0027-8424
- Güngör, T.; Chen, Y.; Golla, R.; Ma, Z.; Corte, J.R.; Northrop, J.P.; Bin, B.; Dickson, J.K.; Stouch, T.; Zhou, R.; Johnson, S.E.; Seethala, R. & Feyen, J.H. (2006). Synthesis and characterization of 3-arylquinazolinone and 3-arylquinazolinethione derivatives as selective estrogen receptor beta modulators. *Journal of Medicinal Chemistry*, Vol.49 No.8, (March 2006), pp. 2440-55, ISSN 0022-2623
- Hengstler, J.G.; Heimerdinger C.K.; Schiffer I.B.; Gebhard S.; Sagemuller, J.; Tanner, B.; Bolt, H.M.; Oesch F. (2002). Dietary topoisomerase II-poisons: contribution of soy products to infant leukemia? *Experimental and Clinical Sciences International online journal for advances in science Journal*, Vol.1, (December 2002), pp. 8-14, ISSN 1611-2156
- Hong, H.; Landauer, M.R.; Foriska, M.A. & Ledney, G.D. (2006). Antibacterial activity of the soy isoflavone genistein. *Journal of Basic Microbiology*, Vol.46, No.4, (August 2006), pp. 329-335, ISSN 0233-111X.
- Howes, J.B.; de Souza, P.L.; West, L.; Huang, L.J. & Howes, L.G. (2011). Pharmacokinetics of phenoxodiol; a novel isoflavone; following intravenous administration to patients with advanced cancer. *BMC Clinical Pharmacology*, Vol.11, (February 2011), pp. 1, ISSN 1472-6904
- Huang, S.Y.; Bolser, D.; Liu, H.Y.; Hwang, T.C. & Zou, X. (2009). Molecular modeling of the heterodimer of human CFTR's nucleotide-binding domains using a protein-protein docking approach. *Journal of Molecular Graphics and Modelling*, Vol.27, No. 7, (April 2009), pp. 822-828, ISSN 1093-3263
- Hukkanen, M.; Platts, L.A.; Lawes, T.; Girgis, S.I.; Konttinen, Y.T. & Goodship, A.E. (2003). Effect of nitric oxide donor hitroglycerin on bone mineral density in a rat model of estrogen deficiency-induced osteopenia. *Bone*, Vol.32, No.2, (February 2003), pp. 142-149, ISSN 8756-3282
- Hwang, T.C. & Sheppard, D.N. (2009). Gating of the CFTR Cl⁻ channel by ATP-driven nucleotide-binding domain dimerisation. *The Journal of Physiology*, Vol.587, No.Pt10, (May 2009), pp. 2151-2161, ISSN 0022-3751
- Imai, Y.; Tsukahara, S.; Asada, S. & Sugimoto, Y. (2004). Phytoestrogens/flavonoids reverse breast cancer resistance protein/ABCG2-mediated multidrug resistance. *Cancer Research*, Vol. 64, No.12, (June 2004), pp. 4346-4352, ISSN: 0008-5472
- Kim, S.; Shin, H.J.; Kim, S.Y.; Kim, J.H.; Lee, Y.S.; Kim, D.H. & Lee, M.O. (2004). Genistein enhances expression of genes involved in fatty acid catabolism through activation of PPAR α . *Molecular and Cellular Endocrinology*, Vol.220, No.1-2, (May 2004), pp. 51-58, ISSN 0303-7207

- Kim, S.; Sohn, I.; Lee, Y.S. & Lee, Y.S. (2005). Hepatic Gene Expression Profiles Are Altered by Genistein Supplementation in Mice with Diet-Induced Obesity *Journal of Nutrition*, Vol.135, No1, (January 2005), pp. 33-41, ISSN 0022-3166
- King-Batoon, A.; Leszczynska, J.M. & Klein, C.B. (2008). Modulation of Gene Methylation by Genistein or Lycopene in Breast Cancer Cells. *Environmental and Molecular Mutagenesis*, Vol.49, No.1, (January 2008), pp. 36-45, ISSN 0893-6692
- Klinge, C. (2000) Estrogen receptor interaction with co-activators and co-repressors. *Steroids*, Vol.65, No.5, (May 2000), pp. 227-251, ISSN, 0039-128X
- Kluger, H.M.; McCarthy, M.M.; Alvero, A.B.; Sznol, M.; Ariyan, S.; Camp, R.L.; Rimm, D.L.; Mor, G. (2007). The X-linked inhibitor of apoptosis protein (XIAP) is up-regulated in metastatic melanoma, and XIAP cleavage by Phenoxodiol is associated with Carboplatin sensitization. *Journal of Translational Medicine*, Vol.5, (January 2007), pp. 6, ISSN, 1479-5876
- Knight, D.C. & Eden, J.A. (1996). A review of the clinical effects of phytoestrogens. *Obstetrics and Gynecology*, Vol.87, No.5Pt2, (May 1996), pp. 897-904, ISSN 1088-5862
- Kohen, F.; Gayer, B.; Kulik, T.; Frydman, V.; Nevo, N.; Katzburg, S.; Limor, R.; Sharon, O.; Stern, N. & Somjen, D. (2007). Synthesis and evaluation of the antiproliferative activities of derivatives of carboxyalkyl isoflavones linked to N-t-Boc-hexylenediamine. *Journal of Medicinal Chemistry*, Vol.50, No.25, (December 2007), pp. 6405-6410, ISSN 0022-2623
- Kostelac, D.; Rechkemmen, G. & Briviba, K. (2003). Phytoestrogens Modulate Binding Response of Estrogen Receptors α and β to the Estrogen Response Element. *Journal of Agricultural and Food Chemistry*, Vol.51, No.26, (December 2003), pp. 7632-7635, ISSN 0021-8561
- Ksycińska, H.; Sobik, B.; Popiołkiewicz, J.; Polkowski, K.; Krzeczyński, P.; Ramza, J.; Pucko, W. & Gryniewicz, G. (2004). Determination of new derivatives of genistein in culture media by liquid chromatography. *Journal of Chromatography B*, Vol.799, No.2, (January 2004), pp. 217-231, ISSN 1570-0232
- Kuiper, G.G.; Lemmen, J.G.; Carlsson, B.; Gorton, J.C.; Safe, S.H.; van der Saag, P.T.; van der Burg, B. & Gustafsson, J.A. (1998). Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. *Endocrinology*, Vol.139, No.10, (October 1998), pp. 4252-4263, ISSN 1945-7170
- Kurzer, M.S. (2002). Hormonal effects of soy in premenopausal women and men. *Journal of Nutrition*, Vol.132, No.3, (March 2002), pp. 570S-573S, ISSN 0022-3166
- Lavigne, J.A.; Takahashi, Y.; Chandramouli, G.V.R.; Liu, H.; Perkins, S.N.; Hursting, S.D. & Wang, T.T.Y. (2008). Concentration-dependent effects of genistein on global gene expression in MCF-7 breast cancer cells: an oligo microarray study *Breast Cancer Research and Treatment*, Vol.110, No.1, (July 2008), pp. 85-98, ISSN 0167-6806
- Lee, W.Y.; Huang, S.C.; Tzeng, C.C.; Chang, T.L.; Hsu, K.F. (2007). Alterations of Metastasis-Related Genes Identified Using an Oligonucleotide Microarray of Genistein-Treated HCC1395 Breast Cancer Cells. *Nutrition and Cancer*, Vol.58, No.2, (October 2007) pp. 239-246, ISSN 0163-5581

- Li, H.Q.; Xue, J.Y.; Shi, L.; Gui, S.Y. & Zhu, H.L. (2008). Synthesis; crystal structure and antimicrobial activity of deoxybenzoin derivatives from genistein. *European Journal of Medicinal Chemistry*, Vol.43, No.3, (March 2008), pp. 662-667, ISSN 0009-4374
- Li, Y.; Che, M.; Bhagat, S.; Ellis, K.L.; Kucuk, O.; Doerge, D.R.; Abrams, J.; Cher, M.L. & Sarkar F.H. (2004). Regulation of Gene Expression and Inhibition of Experimental Prostate Cancer Bone Metastasis by Dietary Genistein. *Neoplasia*, 6: 354-363, ISSN 1476-5586
- Li, Y.; Sarkar, F.H. (2002). Down-regulation of invasion and angiogenesis-related genes identified by cDNA microarray analysis of PC3 prostate cancer cells treated with genistein. *Cancer Letters*, Vol.186, No.2, (December 2002), pp. 157-164, ISSN: 0304-3835
- Lyoun, S.; Hirano, E.; Tujioka, K.; Mawatari, Y.; Hayase, K.; Okuyama, S. & Yokogoshi, H. (2002). Dietary Genistein Affects Brain Protein Synthesis Rates in Ovariectomized Female Rats. *Journal of Nutrition*, Vol.132, No.7, (July 2002), pp. 2055-2058, ISSN 1541-6100
- Manas, E.S.; Xu, Z.B.; Unwalla, R.J. & Somers, W.S. (2004). Understanding the Selectivity of Genistein for Human Estrogen Receptor- β Using X-Ray Crystallography and Computational Methods. *Structure*, Vol.12, No.12, (December 2004), pp. 2197-2207, ISSN 0910-8270
- Mandeville, J.S.; Froehlich, E. & Tajmir-Riahi, H.A. (2009) Study of curcumin and genistein interactions with human serum albumin. *Journal of Pharmaceutical and Biomedical Analysis*, Vol.49, No.2, (February 2009), pp. 468-474, ISSN 0731-708
- Marini, H.; Minutoli, L.; Polito, F.; Bitto, A.; Altavilla, D.; Atteritano, M.; Gaudio, A.; Mazzaferro, S.; Frisina, A.; Frisina, N.; Lubrano, C.; Bonaiuto, M.; D'Anna, R.; Cannata, M.L.; Corrado, F.; Adamo, E.B.; Wilson, S. & Squadrito, F. (2007). Effects of the phytoestrogen genistein on bone metabolism in osteopenic postmenopausal women: a randomized trial. *Annals of Internal Medicine*, Vol.146, No.12, (June 2007), pp. 839-847, ISSN 0003-4819
- Markovits, J.; Linossier, C.; Fosse, P.; Couprie, J.; Pierre, J.; Jacquemin-Sablon, A.; Saucier, J.M.; Le Pecq, J.B. & Larsen, A.K. (1989). Inhibitory effects of the tyrosine kinase inhibitor genistein on mammalian DNA topoisomerase II. *Cancer Research*, Vol.49, No.18, (September 1989), pp. 5111-5117, ISSN: 0008-5472
- Matsuda, H.; Shimoda, H.; Morikawa, T. & Yoshikawa, M. (2001). Phytoestrogens from the roots of *Polygonum cuspidatum* (Polygonaceae): structure-requirement of hydroxyanthraquinones for estrogenic activity. *Bioorganic & Medicinal Chemistry Letters*, Vol.11, No.14, (July 2001), pp. 839-842, ISSN 0960-894X
- Matsumoto, T.; Kobayashi, T.; Kikuchi, T.; Honda, T. & Kamata, K. (2005). Effects of dual-action of genistein derivatives on relaxation in rat aorta. *Journal of Smooth Muscle Research*, Vol.41, No.1, (February 2005), pp. 23-33, ISSN 0916-8737
- Melani, R.; Tomati, V.; Galiotta, L.J.V. & Zegarra-Moran, O. (2010). Modulation of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Activity and Genistein Binding by Cytosolic pH. *The Journal of Biological Chemistry*, Vol.285, No.53, (December 2010), pp. 41591-41596, ISSN 0021-9258

- Messina, M. (1995). Modern applications for an ancient bean: soybeans and the prevention and treatment of chronic disease. *Journal of Nutrition*, Vol.125, No.3 Supplement, (March 1995), pp. 567S-569S, ISSN: 0022-3166
- Messinger, Y.; Yanishevski, Y.; Ek, O.; Zeren, T.; Waurzyniak, B.; Gunther, R.; Chelstrom, L.; Chandan-Langlie, M.; Schneider, E.; Myers, D.E.; Evans, W. & Uckun, F.M. (1998). In vivo toxicity and pharmacokinetic features of B43 (anti-CD19)-genistein immunoconjugate in nonhuman primates. *Clinical Cancer Research*, Vol.4, No.1, (January 1998), pp. 165-170, ISSN: 1078-0432
- Mewshaw, R.E.; Bowen, S.M.; Harris, H.A.; Xu, Z.B.; Manas, E.S. & Cohn, S.T. (2007). ERbeta ligands. Part 5: synthesis and structure-activity relationships of a series of 4'-hydroxyphenyl-aryl-carbaldehyde oxime derivatives. *Bioorganic & Medicinal Chemistry*, Vol.17, No.4, (February 2007), pp. 902-906, ISSN 0968-0896
- Miller, M.R. & Megson, I.L. (2007). Recent developments in nitric oxide donor drugs. *British Journal of Pharmacology*, Vol.151, No.3, (June 2007), pp. 305-321, ISSN 0007-1188
- Mukherjee, S; Acharya, B.R.; Bhattacharyya, B. & Chakrabarti, G. (2010). Genistein arrests cell cycle progression of A549 cells at the G(2)/M phase and depolymerizes interphase microtubules through binding to a unique site of tubulin. *Biochemistry*, Vol.49, No.8, (March 2010), pp. 1702-1712, ISSN 0955-2863
- Naciff, J.M.; Jump, M.L; Torontali, S.M.; Carr, G.J.; Tiesman, JP.; Overmann G.J. & Daston G.P. (2002). Gene Expression Profile Induced by 17a-Ethynyl Estradiol; Bisphenol A; and Genistein in the Developing Female Reproductive System of the Rat. *Toxicological Sciences*, Vol.68, No.1, (July 2002), pp. 184-199, ISSN 1096-0929
- Naguleswaran, A.; Spicher, M.; Vonlaufen, N.; Ortega-Mora, LM.; Torgerson, P.; Gottstein, B. & Hemphill, A. (2006). In Vitro Metacestodicidal Activities of Genistein and Other Isoflavones against *Echinococcus multilocularis* and *Echinococcus granulosus*. *Antimicrobial Agents and Chemotherapy*, Vol.50, No.11, (November 2006), pp. 3770-3778, ISSN: 0066-4804
- Niculescu, M.D.; Pop, E.A.; Fischer, L.M. & Zeisel, S.H. (2007). Dietary isoflavones differentially induce gene expression changes in lymphocytes from postmenopausal women who form equol as compared with those who do not. *Journal of Nutritional Biochemistry*, Vol.18, No.6, (June 2007), pp. 380- 390, ISSN 0955-2863
- Okura, A.H.; Arakawa, H.; Oka, H.; Yoshinari, T. & Moden, Y. (1988). Effect of genistein on topoisomerase activity and on the growth of [Val 12]Ha-ras-transformed NIH 3T3 cells. *Biochemical and Biophysical Research Communications*, Vol.157, No.1, (November 1988), pp.183-189, ISSN 0006-291X
- Paoletta, S.; Steventon, G.B.; Wildeboer, D.; Ehrman, T.M.; Hylands, P.J. & Barlow, D.J. (2008). Screening of herbal constituents for aromatase inhibitory activity. *Bioorganic & Medicinal Chemistry*, Vol.16, No18, (September 2008), pp. 8466-8470, ISSN 0968-0896
- Perez, M.; Real, R.; Mendoza, G.; Merino, G.; Prieto, J.G. & Alvarez, A.I. (2009). Milk secretion of nitrofurantoin as a specific BCRP/ABCG2 substrate in assaf sheep: modulation by isoflavones. *Journal of Veterinary Pharmacology and Therapeutics*, Vol.32, No5, (October 2009), pp. 498-502, ISSN 0140-7783

- Pie, J.E.; Park, J.H.; Park, Y.H.; Ryu, Y.M.; Kim, K.N.; Suh, S.W.; Becker, K.G.; Cho-Chung, Y.S. & Kim, M.K. (2006). Effect of genistein on the expression of bone metabolism genes in ovariectomized mice using a cDNA microarray. *Journal of Nutritional Biochemistry*, Vol.17, No.3, (March 2006), pp. 157-164, ISSN: 0955-2863
- Pike, A.C.W.; Brzozowski, A.M.; Hubbard, R.E.; Bonn, T.; Thorsell, A.G.; Engstrom, O.; Ljunggren, J.; Gustafsson, J.Å. & Carlquist, M. (1999). Structure of the ligand-binding domain of oestrogen receptor beta in the presence of a partial agonist and a full antagonist. *The European Molecular Biology Organization Journal*, Vol.18, No.17, (September 1999), pp. 4608-4618, ISSN:0261-4189
- Polkowski, K.; Popiołkiewicz, J.; Krzeczyński, P.; Ramza, J.; Pucko, W.; Zegrocka-Stendel, O.; Boryski, J.; Skierski, J.S.; Mazurek, A.P. & Gryniewicz, G. (2004). Cytostatic and cytotoxic activity of synthetic genistein glycosides against human cancer cell lines. *Cancer Letters*, Vol.203, No.1, (January 2004), pp. 59-69, ISSN 0304-3835
- Popiołkiewicz, J.; Polkowski, K.; Skierski, J.S. & Mazurek, A.P. (2005). In vitro toxicity evaluation in the development of new anticancer drugs-genistein glycosides. *Cancer Letters*, Vol.229, No.1, (November 2005), pp. 67-75, ISSN 0304-3835
- Radovic, B.; Mentrup, B. & Kohrle, J. (2006). Genistein and other soya isoflavones are potent ligands for transthyretin in serum and cerebrospinal fluid. *British Journal of Nutrition*, Vol.95, No.6, (June 2006), pp. 1171-1176, ISSN 0022-3166
- Rao, G.N. (1997). Protein Tyrosine Kinase Activity Is Required for Oxidant-Induced Extracellular Signal-Regulated Protein Kinase Activation and c-fos and c-jun Expression. *Cellular Signalling*, Vol.9, No.2, (February 1997), pp. 181-187, ISSN 0898-6568
- Reginster, J.Y. (2011). Antifracture efficacy of currently available therapies for postmenopausal osteoporosis. *Drugs*, Vol.71, No.1, (January 2011), pp. 65-78, ISSN 0012-6667
- Relic, B.; Zeddou, M.; Desoroux, A.; Beguin, Y.; de Seny, D. & Malaise, M.G. (2009). Genistein induces adipogenesis but inhibits leptin induction in human synovial fibroblasts. *Laboratory Investigation*, Vol.89, No.7, (July 2009), pp. 811-822, ISSN: 0023-6837
- Rice, L.; Handayani R.; Cui, Y.; Medrano, T.; Samedi, V.; Baker, H.; Szabo, N.J.; Rosser, C.J.; Goodison, S.; Shiverick, K.T. (2007). Soy Isoflavones Exert Differential Effects on Androgen Responsive Genes in LNCaP Human Prostate Cancer Cells. *Journal of Nutrition*, Vol.137, No.4, (April 2007), pp. 964-972, ISSN: 0022-3166
- Rimbach, G.; Boesch-Saadatmandi, C.; Frank, J.; Fuchs, D.; Wenzel, U.; Daniel, H.; Hall, W.L. & Weinberg, P.D. (2008). Dietary isoflavones in the prevention of cardiovascular disease - A molecular perspective. *Food and Chemical Toxicology*, Vol.46, No.4, (April 2008), pp. 1308-1319, ISSN 0278-6915
- Rusin A.; Gogler, A.; Głowala-Kosińska, M.; Bochenek, D.; Gruca, A.; Gryniewicz, G.; Zawisza, J.; Szeja, W. & Krawczyk, Z. (2009). Unsaturated genistein disaccharide glycoside as a novel agent affecting microtubules. *Bioorganic & Medicinal Chemistry Letters*, Vol.19, No.17, (September 2009), pp. 4939-4943, ISSN 0960-894X

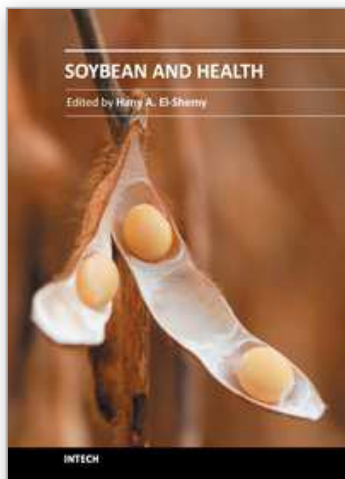
- Rusin, A.; Krawczyk, Z.; Gryniewicz, G.; Gogler, A.; Zawisza-Puchałka, J. & Szeja, W. (2010). Synthetic derivatives of genistein; their properties and possible applications. *Acta Biochimica Polonica*, Vol.57, No.1, (March 2010), pp. 23-34, ISSN 0001-527X
- Rusin, A.; Zawisza-Puchałka, J.; Kujawa, K.; Gogler-Piğłowska, A.; Wietrzyk, J.; Świtalska M.; Głowala-Kosińska, M.; Gruca, A.; Szeja, W.; Krawczyk, Z. & Gryniewicz, G. (2011). Synthetic conjugates of genistein affecting proliferation and mitosis of cancer cells. *Bioorganic & Medicinal Chemistry*, Vol.19, No.1, (January 2011), pp. 295-305, ISSN 0960-894X
- Saif, M.W.; Tytler, E.; Lansigan, F.; Brown, D.M. & Husband, A.J. (2009). Flavonoids; phenoxodiol; and a novel agent; triphendiol; for the treatment of pancreaticobiliary cancers. *Expert Opinion on Investigational Drugs*, Vol.18, No.4, (April 2009), pp. 469-79, ISSN 1354-3784
- Salam, N.K.; Huang, T.H.W.; Kota, B.P.; Kim, M.S.; Li, Y. & Hibbs, D.E. (2008). Novel PPAR-gamma Agonists Identified from a Natural Product Library: A Virtual Screening; Induced-Fit Docking and Biological Assay Study. *Chemical Biology & Drug Design*, Vol.71, No.1, (January 2008), pp. 57-70, ISSN 1747-0277
- Sapi, E.; Alvero, A.B.; Chen, W.; O'Malley, D.; Hao, X.Y.; Dwipoyono, B.; Garg, M.; Kamsteeg, M.; Rutherford, T. & Mor, G. (2004). Resistance of ovarian carcinoma cells to docetaxel is XIAP dependent and reversible by phenoxodiol. *Oncology Research*, Vol.14, No.11-12, (2004), pp. 567-78, ISSN 0965-0407
- Schulte, G. & Fredholm, B.B. (2002). Diverse inhibitors of intracellular signalling act as adenosine receptor antagonists. *Cellular Signalling*, Vol. 14, No.2, (February 2002), pp. 109-113, ISSN 0898-6568
- Selvaraj, V.; Bunick, D.; Finnigan-Bunick, C.; Johnson, R.W.; Wang, H.; Liu, L. & Cooke, P.S. (2005) Gene Expression Profiling of 17 β -Estradiol and Genistein Effects on Mouse Thymus. *Toxicological Sciences*, Vol.87, No.1, (September 2005), pp. 97-112, ISSN 1096-0929
- Setchell, K.D.; Brown, N.M.; Desai, P.; Zimmer-Nechemias, L.; Wolfe, B.E.; Brashear, W.T.; Kirschner, A.S.; Cassidy, A. & Heubi, J. E. (2001). Bioavailability of pure isoflavones in healthy humans and analysis of commercial soy isoflavone supplements. *Journal of Nutrition*, Vol.131, No.4 Supplement, (April 2001), pp. 1362S-1375S, ISSN 0002-9165
- Silasi D.A.; Alvero, A.B.; Rutherford, T.J.; Brown, D. & Mor, G. (2009). Phenoxodiol: pharmacology and clinical experience in cancer monotherapy and in combination with chemotherapeutic drugs. *Expert Opinion on Pharmacotherapy*, Vol.10, No.6, (April 2009), pp. 1059-1067, ISSN 1465-6566
- Somjen, D.; Amir-Zaltsman, Y.; Gayer, B.; Kulik, T.; Knoll, E.; Stern, N.; Lu, L.J.; Toldo, L. & Kohen, F. (2002). 6-Carboxymethyl genistein: a novel selective oestrogen receptor modulator (SERM) with unique; differential effects on the vasculature; bone and uterus. *Journal of Endocrinology*, Vol.173, No.3, (June 2002), pp. 415-427, ISSN 0022-0795
- Somjen, D.; Stern, N.; Knoll, E.; Sharon, O.; Gayer, B. & Kulik, T. (2003). Carboxy derivatives of isoflavones as affinity carriers for cytotoxic drug targeting in adrenocortical

- H295R carcinoma cells. *Journal of Endocrinology*, Vol.179, No.3, (December 2003), pp. 395-403, ISSN 0022-0795
- Stachulski, A.V.; Berry, N.G.; Low, A.C.L.; Moores, S.L.; Row, E.; Warhurst, D.C.; Adagu, I.S. & Rossignol, J.F. (2006). Identification of Isoflavone Derivatives as Effective Anticryptosporidial Agents in Vitro and in vivo. *Journal of Medicinal Chemistry*, Vol.49, No.4, (February 2006), pp. 1450-1454, ISSN 0022-2623
- Suetsugi, M.; Su, L.; Karlsberg, K.; Yuan, Y.C. & Chen, S. (2003). Flavone and Isoflavone Phytoestrogens Are Agonists of Estrogen-Related Receptors. *Molecular Cancer Research*, Vol.1, No.13, (November 2003), pp. 981-991, ISSN 1541-7786
- Takahashi, Y.; Lavigne, J.A.; Hursting, S.D.; Chandramouli, G.V.R.; Perkins, S.N.; Barrett, J.T.C.; Wang, T.Y. (2004). Using DNA microarray analyses to elucidate the effects of genistein in androgen-responsive prostate cancer cells: Identification of novel targets. *Molecular Carcinogenesis*, Vol.41, No.2, (October 2004), pp. 108-119, ISSN 0899-1987
- Tanenbaum, D.M.; Wang, Y.; Williams, S.P. & Sigler, P.B. (1998). Crystallographic comparison of the estrogen and progesterone receptor's ligand binding domains. *The Proceedings of the National Academy of Sciences*, Vol.95, No.11, (May 1998), pp. 5998-6003, ISSN 0027-8424
- Traxler, P.; Trinks, U.; Buchdunger, E.; Mett, H.; Meyer, T.; Müller, M.; Regenass, U.; Rösel, J. & Lydon, N. (1995). [(Alkylamino)methyl]acrylophenones: potent and selective inhibitors of the epidermal growth factor receptor protein tyrosine kinase. *Journal of Medicinal Chemistry*, Vol.38, No.13, (June 1995), pp. 2441-2248, ISSN 0022-2623
- Trivella, D.B.; Bleicher, L.; Palmieri, L.C.; Wiggers, H.J.; Montanari, C.A.; Kelly, J.W.; Lima, L.M.; Foguel, D. & Polikarpov, I. (2010). Conformational differences between the wild type and V30M mutant transthyretin modulate its binding to genistein: Implications to tetramer stability and ligand-binding. *Journal of Structural Biology*, Vol.170, No.3, (June 2010), pp. 522-531, ISSN 1047-8477.
- Uckun, F.M.; Messinger, Y.; Chen, C.L.; O'Neill, K.; Myers, D.E.; Goldman, F.; Hurvitz, C.; Casper, J.T. & Levine, A. (1999). Treatment of therapy-refractory B-lineage acute lymphoblastic leukemia with an apoptosis-inducing CD19-directed tyrosine kinase inhibitor. *Clinical Cancer Research*, Vol.5, No.12, (December 1999), pp. 3906-3913, ISSN 1078-0432
- Uckun, F.M.; Narla, R.K.; Zeren, T.; Yanishevski, Y.; Myers, D.E.; Waurzyniak, B.; Ek, O.; Schneider, E.; Messinger, Y.; Chelstrom, L.M.; Gunther, R. & Evans, W. (1998). In vivo toxicity; pharmacokinetics; and anticancer activity of Genistein linked to recombinant human epidermal growth factor. *Clinical Cancer Research*, Vol.4, No.5, (March 1998), pp. 1125-1134, ISSN 1078-0432
- Ulanowska, K.; Majchrzak, A.; Moskot, M.; Jakóbkiewicz-Banecka, J. & Węgrzyn, G. (2007). Assessment of antibacterial effects of flavonoids by estimation of generation times in liquid bacterial cultures. *Biologia; Bratislava. Section Cellular and Molecular Biology*, Vol.62, No.2, (April 2007), pp. 132-135, ISSN: 1335-6399
- Ulanowska, K.; Tkaczyk, A.; Konopa, G. & Węgrzyn, G. (2006). Differential antibacterial activity of genistein arising from global inhibition of DNA; RNA and protein

- synthesis in some bacterial strains. *Archives of Microbiology*, Vol.184, No.5, (January 2006), pp. 271-278, ISSN 0302-8933
- Vanhees, K.; Coort, S.; Ruijters, E.J.B.; Godschalk, R.W.L.; van Schooten, F.J. & Barjesteh van Waalwijk van Doorn-Khosrovani, S. (2011). Epigenetics: prenatal exposure to genistein leaves a permanent signature on the hematopoietic lineage *Federation of American Societies for Experimental Biology Journal*, Vol.25, No.2, (February 2011), pp. 797-807, ISSN 0892-6638
- Velders, M.; Solzbacher, M.; Schleipen, B.; Laudénbach, U.; Fritze-meier, K.H.; Diela, P.; (2010). Estradiol and genistein antagonize the ovariectomy effects on skeletal muscle myosin heavy chain expression via ER- β mediated pathways. *Journal of Steroid Biochemistry & Molecular Biology*, Vol.120, No.1, (May 2010), pp. 53-59, ISSN 0960-0760
- Vera, R.; Sánchez, M.; Galisteo, M.; Villar, I.C.; Jimenez, R.; Zarzuelo, A.; Pérez-Vizcaíno, F. & Duarte, J. (2007). Chronic administration of genistein improves endothelial dysfunction in spontaneously hypertensive rats: involvement of eNOS; caveolin and calmodulin expression and NADPH oxidase activity. *Clinical Science (London)*, Vol.112, No.3, (February 2007), pp. 183-191, ISSN 0143-5221
- Vera, J.C.; Reyes, A.M.; Cárcamo, J.G.; Velásquez, F.V.; Rivas, C.I.; Zhang, R.H.; Strobel, P.; Iribarren, R.; Scher, H.I.; Slebe, J.C. & Golde D.W. (1996). Genistein is a natural inhibitor of hexose and dehydroascorbic acid transport through the glucose transporter; GLUT1. *Journal of Biological Chemistry*, Vol.271, No.15, (April 1996), pp. 8719-8724, ISSN 0021-9258
- Verdrengh, M.; Collins, L.V.; Bergin, P. & Tarkowski, A. (2004). Phytoestrogen genistein as an anti-staphylococcal agent. *Microbes and Infection*, Vol.6, No.1, (January 2004), pp. 86-92, ISSN 1286-4579
- Wang SF, Jiang Q, Ye YH, Li Y, Tan RX (2005) Genistein derivatives as selective estrogen receptor modulators: Sonochemical synthesis and in vivo anti-osteoporotic action. *Bioorganic & Medicinal Chemistry*, Vol.13, No.16, (August 2005), pp. 4880-4890, ISSN: 09680896
- Wang, F.; Zeltwanger, S.; Yang, I.C.H.; Nairn, A.C. & Hwang T.C. (1998). Actions of genistein on cystic fibrosis transmembrane conductance regulator channel gating: evidence for two binding sites with opposite effects. *The Journal of General Physiology*, Vol.111, No.3, (March 1998), pp. 477-490, ISSN 0022-1295
- Wang, J.; Shang, F.; Jing, R.; Liu, L.; Wang, S.; Hou, J.; Huan, M. & Mei, Q. (2007). Nitric oxide-donating genistein prodrug: design; synthesis and bioactivity of MC3T3-E1 cells. *Journal of Pharmacological Sciences*, Vol.104, No1, (May 2007), pp. 82-89, ISSN 0022-3549
- Węgrzyn, G.; Jakóbkiewicz-Banecka, J.; Gabig-Cimińska, M.; Piotrowska, E.; Narajczyk, M.; Kloska, A.; Malinowska, M.; Dziedzic, D.; Gołębiewska, I.; Moskot, M. & Węgrzyn, A. (2010). Genistein: a natural isoflavone with a potential for treatment of genetic diseases. *Biochemical Society Transactions*, Vol.38, No.2, (April 2010), pp. 695-701, ISSN 0300-5127
- Wimalawansa, S.J. (2000). Nitroglycerin therapy is as efficacious as standard estrogen replacement therapy (Premarin) in prevention of oophorectomy-induced bone loss:

- a human pilot clinical study. *Journal of Bone and Mineral Research*, Vol.15, No.11, (November 2000), pp. 2240-2244, ISSN 0884-0431
- Xie, H.Z.; Li, L.L.; Ren, J.X.; Zou, J.; Yang, L.; Wei, Y.Q.; Yang, S.Y. (2009). Pharmacophore modeling study based on known spleen tyrosine kinase inhibitors together with virtual screening for identifying novel inhibitors. *Bioorganic & Medicinal Chemistry Letters*, Vol.19, No.7, (April 2009) pp. 1944-1949, ISSN 0968-0896
- Xu, L.; Ding, Y.; Catalona, W.; Yang, X.J.; Anderson, W.F.; Jovanovic, B.; Wellman, K.; Killmer, J.; Huang, X.; Scheidt, K.A.; Montgomery, R.B. & Bergan, R.C. (2009). MEK4 Function; Genistein Treatment; and Invasion of Human Prostate Cancer Cells. *Journal of the National Cancer Institute*, Vol.101, No.16, (August 2009), pp. 1141 - 1155, ISSN 0027-8874
- Yuan, J.L.; Liu, H.; Kang, X; Lv, Z. & Zou, G.L. (2008). Characteristics of the isomeric flavonoids apigenin and genistein binding to hemoglobin by spectroscopic methods. *Journal of Molecular Structure*, Vol.891, No.1-2, (November 2008), pp. 333-339, ISSN 0022-2860
- Zhang, L.N.; Cao, P.; Tan, S.H.; Gu, W.; Shi, L. & Zhu, H.L. (2008a). Synthesis and antimicrobial activities of 7-O-modified genistein derivatives. *European Journal of Medicinal Chemistry*, Vol.43, No.7, (July 2008), pp. 1543-1551, ISSN: 0223-5234
- Zhang, S.; Yang, X.; Morris & M.E. (2004). Flavonoids are inhibitors of breast cancer resistance protein (ABCG2)-mediated transport. *Molecular Pharmacology*, Vol.65, No.5, (May 2004), pp. 1208-1216, ISSN 0026-895X
- Zhang, Y.; Li, X.L.; Yao, X.S. & Wong, M.S. (2008b). Osteogenic Activities of Genistein Derivatives were Influenced by the Presence of Prenyl Group at Ring A. *Archives of Pharmacal Research*, Vol.31, No.12, (December 2008), pp. 1534-1539, ISSN 0253-6269

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Soybean and Health

Edited by Prof. Hany El-Shemy

ISBN 978-953-307-535-8

Hard cover, 502 pages

Publisher InTech

Published online 12, September, 2011

Published in print edition September, 2011

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How to reference

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Aleksandra Rusin and Zdzislaw Krawczyk (2011). Genistein Derivatization – From a Dietary Supplement to a Pharmaceutical Agent, *Soybean and Health*, Prof. Hany El-Shemy (Ed.), ISBN: 978-953-307-535-8, InTech, Available from: <http://www.intechopen.com/books/soybean-and-health/genistein-derivatization-from-a-dietary-supplement-to-a-pharmaceutical-agent>

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