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Gossypin: A phytochemical of multispectrum potential

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ABSTRACT

Nature is the source of the various raw chemicals in the form of oils, food supplement, nutraceuticals, and colour pigments. A lot of presently existing drugs available in the market mainly belong to the natural sources including the plants, animal, microorganism, minerals and marine source. Flavonoids, benzo-c-pirone derivatives are one of the main secondary flavonoid liable for the different shades of flowers like orange, yellow and red color. More than 4000 flavonoids like flavanols, flavonols, isoflavones, flavanones, flavanonols and flavones are found in the different edible plants which are also found in the regular human diet. Flavonoids are present in vegetables, spices, tea, whole grains, fruits, wine, herbs and seeds. Gossypin, a flavonol glucoside, is present in the flowers of different plants like *Gossypium indicum*, *Hibiscus esculentus* and *Hibiscus vitifolius* and is one of the major chemical of plants belonging to 'Malvaceae' family. In the present review, we have collected all the information of gossypin and found that it has antioxidant, anti-inflammatory, anticancer, anticataract, antidiabetic, analgesic and hepatoprotective activities. It also protects against beta-amyloid induced toxicity. The information provided in the present review will be beneficial to the researchers of the various field of science for the development of better alternate for various disorders. On the basis of the presented database of this review we can conclude that gossypin has various beneficial effects and it could be used for the treatment of various disorders.

1. Introduction

Phytochemicals are the main active chemical of plants and its different parts such as leaves, fruits, flower, and seeds and sometimes even in the whole vegetables. Phytochemicals have the potentials to treat and cure all types of the degenerative and chronic diseases in the human being and other species of the earth. The beneficial effects of foods are mainly because of the presence of different macro as well as micro nutrients (vitamins and minerals). From the research, it has found that diet containing higher amount of vegetables and fruit could protect our body from various diseases including some complicated one such as atherosclerosis and cancer. Epidemiological studies have also supported the higher intake of dietary flavonoid in case of cardiovascular diseases[1]. Biological processes involved enzymatic reactions, cell signaling pathways and these are affected by many chemical constituents of food substances, so these phytochemicals could affect the human health either

positively or negatively. Plants have their own defense mechanism for their own protection and flavonoids play an important role in the same which will be beneficial for their growth and development[2]. There are various properties of phenolic and flavonoid compounds which are important for fruits and its derived products in terms of their organoleptic, the nutritional and commercial properties. On the basis of several studies, it is also found that high polyphenolic contents in the food substances are beneficial for cancer, cardiovascular, and neurodegenerative disorders. In addition to these biological important aspects, these compounds are also beneficial in the food preservation compare to chemically derived product[3]. The Mediterranean diets have more beneficial health aspects, that's why in Greece, the various greens vegetables are consumed in different form[4]. Concentration of flavonoid in the plants mainly depends on the phyla, order, family and species variations and glycosidal form of flavonols is one of the main phytochemicals in the fruits and leafy vegetables. Flavonol glycosides are present in the different parts of the plants such as in the outer parts of skin and peel, leaves and flowers and in some special cases it is also present in some parts of plant below the soil surface[5]. Human diet comprises polyphenolic compounds and flavonoids which are one of the most common active components in the plants. In the human diet, flavonoids comes from vegetables, fruits, fruit juices, cereals, wine and tea, and after ingestion of these flavonoids, it metabolizes in the

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liver, in the large and small intestines and also in some cells[6].

1.1. Biosynthesis of flavonoidal compounds

Flavonoids are one of the important secondary metabolite found to be present in the nature in the form of polyphenolic substances with low-molecular-weight. Flavonoids are mainly formed through the intermediates of the phenylalanine and acetic acid derivative, and formation of phenylalanine from phenylpyruvate will be the first and important step and then phenylalanine will be converted to trans-cinnamic acid and after hydrolysis to *p*-coumaric acid having six carbon moieties (C-9). In the subsequent step C-15 chalcone will be generated by the condensation of this C-9 acid with three unit of malonyl-coA. Further their will be the formation of 3, 4-dioflavonoids and 3-hydroxyflavonoids via ring closure and hydration. So at the last the flavonoid will be derived using phenylalanine as a starting material which will consist three phenolic rings A, B, and C[5] (Figure 1).

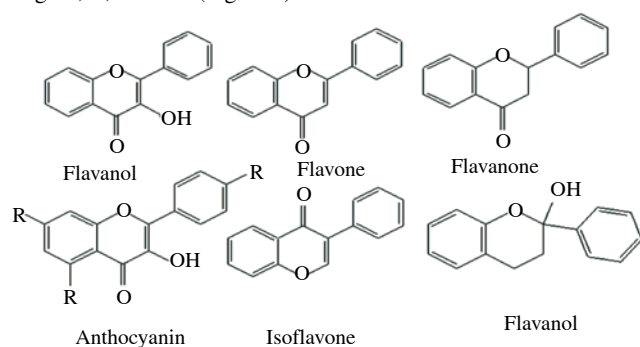


Figure 1. Chemical structure of different flavonoids.

1.2. Chemical structure and classification of flavonoids

Flavonoids are low molecular weight polyphenolic compound having flavan nucleus and mainly composed of three phenolic rings A, B, and C. In the nature flavonoids are categorized into different classes of compound as per their chemical class of anthocyanidins, flavones, isoflavones, flavonols, dihydroflavonols, flavanones, catechins, and chalcones (Figure 1)[7]. Flavonoids were also categorized into different classes on the basis of their glycosidic side groups, arrangements of methoxy and hydroxyl group and their A and B ring conjugation[8]. Flavonoids are also divided into different classes based upon the oxidation level of C ring and substitution in the A, B, and C rings[5]. If there is the presence of hydroxyl group in position C-3 of the C ring it will generate 3-hydroxyflavonoids and examples are leucoanthocyanidins, flavonols, catechins and anthocyanidins. Sometimes because of the combinations of flavonoidal aglycones and sugars, it also generates many flavonoids[9] (Figure 1). The main flavonoids which are present in the human diet are genistein, quercetin, flavonols, apigenin, luteolin, cyanidin, kaempferol, epigallocatechin, pelargonidin, daidzein, hesperetin, naringenin, (+)-catechin, (-)-epicatechin, epigallocatechin gallate, and malvidin as these will not be able to produce by human and animal internally[6]. O-glycosides is one of the major class of dietary flavonoids and galactose, glucose, glucorhamnose, arabinose and rhamnose are main glycone part in the same[8]. Flavonoids of different chemical moieties have different biological properties and among all the known flavonoids in the nature, flavonols are the most important after quercetin, myricetin and kaempferol. Flavanones and flavones are the basic chemical moiety of citrus fruits and celery where as strawberry and soy foods contain anthocyanins and

isoflavones[2].

1.3. Overview of flavonoid

Flavonoids are polyphenolic compounds synthesized in plants from phenylalanine and occur naturally in bark, vegetables, fruit, seeds, flowers, and nuts. Flavonoids have various pharmacological activities such as antiinflammatory, antibacterial, antiallergic, antiviral, and vasodilatory actions. Flavonoids inhibit lipoxygenase enzyme, capillary permeability, cyclooxygenase, lipid peroxidation, fragility and platelet aggregation[7,10]. Antioxidant potency of flavonoid mainly depends upon the chemical, physical, and structural properties. Due to their antioxidant property, it will counteract the free radicals and prevent various diseases. Flavonoids possess hepatoprotective, antioxidant, antithrombotic, antiallergic, anticarcinogenic and neuroprotective activities[11]. In the nature till so far more than 4000 flavonoids have already been identified which are mainly distributed in the different parts of the plant such as flowers, bark, leaves and seeds. Flavonoids also play an important role in the plant defence mechanism and protect plants against pathogens, ultraviolet radiation and herbivores. In human diet, wines, berries, and vegetables are main sources of flavonoids[8]. Flavonoids inhibit reactive radicals, improve blood circulation, reduce inflammation, enhance antioxidative enzymes and inhibit cancer cells growth and platelet aggregation[12]. High intake of vegetables and fruit decreased cancer and coronary heart disease mortality rate in human beings[13]. Flavonoid also shows cytotoxic, antiviral, antioxidant, oestrogenic, antiinflammatory and antitumoral activity in human beings[14]. In France and Switzerland many preparation made through different flavonoidal compounds which have been used to treat circulation and peripheral disorders. More than hundred preparations are available in the market which contains different flavonoidal component such as hesperidin, cyanidanol, leucocyanidin, diosmetin, troxerutin and rutin[7]. Flavonoids improve neurological health via interaction with intracellular neuronal and glial signaling pathways and reduce neuronal damage mainly induced by neurotoxic substances[6]. On the basis of the various report published in the papers, we can conclude that pharmaceuticals importance of flavonoids is more beneficial compared to their health benefits[7].

1.4. Dietary intake and food sources of flavonoids

Flavonoids play an important role in the human health and in the USA the average intake of dietary flavonoids is approximately 1 g/day, whereas in the Netherlands it is estimated to be 23 mg/day. Quercetin was found to be the most dietary flavonoid after luteolin, kaempferol, apigenin and myricetin. In case of different plants and vegetable product, the concentration of these flavonoids differed and was found to be 48%, 29% and 7% in tea, onions and apples respectively. Further, red wine also contained significance amount of flavonoid and it was found to be 22.5 mg/L[7]. In the normal human diet if the total consumption of the flavonoid is 2 g in a day, it will be beneficial for the human health[2].

1.5. Overview of flavonols

Flavonols are one of the major polyphenolic compounds found in the nature which contain two benzene rings joined by a linear three carbon chain and represent with C6-C3-C6. Presence of -OH moieties and resonance of electrons between A- and B-rings is important for antioxidant activities and other biological activities

of flavonols[15]. Colour of wines is mainly due to the presence of flavonols which are yellow pigments and also responsible for antioxidant activity of same[16]. Flavonols are present in various types of flavonoids which have colour from white to yellow and kaempferol, myricetin, isorhamnetin and quercetin are the examples[17]. Presence of sugar moiety in the aglycon portion influences the bioavailability of flavonols. Aglycons form of flavonols in the diet have poor bioavailability compared to the glycosidal form and absorption of flavonol glycosides also depends on species as well as sugar moieties location in the molecules[12]. Flavonols play various functions in higher plants such as they can protect the plants against damages caused by visible and UV radiation[18]. Flavonols have various uses in the health as they have anticarcinogenic and antioxidant potential and effective in case of coronary heart disease. In western countries, onions, apples, tea and berries are the major source of flavonols[19]. Quercetin is the most common flavonol in the diet and it is present in various vegetables, fruits, tea, wine and especially onions. In Italy, major source of quercetin is wine whereas in Greece, United States, Finland, and Yugoslavia, onions and apples are one of the best sources. For an adult, the daily intake of quercetin was found to be 3–38 mg whereas in the United States flavonols and flavones intake was found to be 20–22 mg/day[9].

1.6. Overview of gossypin

Gossypin (3, 30, 40, 5, 7, 8-hexahydroxyflavone 80-glucoside) is a flavonol glucoside mainly present in the flowers of various species of *Hibiscus* like *Hibiscus vitifolius* (*H. vitifolius*), *Gossypium indicum*, and *Hibiscus esculentus*. Gossypin exhibits antioxidant, antiinflammatory, anticancer and antidiabetic activities. Presence of different groups in the basic chemical structure affects solubility and water solubility of gossypin, which is mainly due to the presence of a glucose moiety in its chemical structure[10]. In the nature, gossypin is present in different plants of Malvaceae family[20]. Presence of glucose moiety in the gossypin chemical structure makes it soluble in water whereas it is also sparingly soluble in alcohol. Gossypin has antiinflammatory, antioxidant, analgesic, hepatoprotective and hypoglycemic activities. Moreover it also reduces the toxicity of dermally induced lipid peroxidation and delays the onset of cataract formation in rats[11,21,22]. Gossypin suppresses beta-amyloid induced toxicity and has antioxidant activity, mediates antinociception and protects against carbon tetrachloride-induced toxicity. It inhibits cell proliferation in K562, L929 and HT29 tumor cell lines. It also inhibited angiogenesis and control the growth of Ehrlich's ascites carcinoma. Further gossypin also showed anticarcinogenic activity in the DMBA-croton oil-induced papilloma in the rodent's model[23].

2. Pharmacological activities of gossypin

2.1. Antidiabetic activity of gossypin

Effect of gossypin in streptozotocin induced diabetes rats was investigated at 20 mg/kg for 30 days model. In the gossypin treated group there is the decreased level of blood glucose and HbA1c levels and the increased level of plasma insulin and hemoglobin which signified its antidiabetic potential. Further liver and muscles glycogen content was also significantly improved whereas blood urea level and plasma protein level were also normalized in the treated groups. Thus from these results, we can conclude that gossypin has antidiabetic potential[24]. To investigate the effect of flavonoids on intestinal

facilitated glucose transporters (GLUT2), basolateral membrane vesicles (BLMV) isolated from the rat jejunum were used to measure the glucose uptake in the presence of flavonoids and result showed that gossypin inhibited glucose uptake[25].

2.2. Antiinflammatory activity of gossypin

Antiinflammatory and antinociceptive activities of gossypin, chrysin, methyl hesperidin and procumbentin were investigated and found that gossypin and procumbentin have antinociceptive activity whereas gossypin showed antiinflammatory activity. Further *in vitro* studies also revealed that both procumbentin and gossypin have COX-2 inhibitory activity[26]. In another study, oral administration of flavonoids including gossypin inhibited paw oedema in carrageenin induced oedema in mice[27]. The effect of flavonoids on the arachidonic acid metabolism in sonicated sheep platelets was studied. Result showed that 12-lipoxygenase was inhibited by gossypin, hypolaetin-8-O-beta-D-glucoside, cirsiolol, hypolaetin, gossypetin, leucocyanidol and hibifolin. These results revealed that lipoxygenase inhibition could play an essential role in the antiinflammatory activity[28].

2.3. Anticancer activity of gossypin

Effects of gossypin on human glioma U251 cells were investigated to know its anticancer potential and were found to have cell proliferation inhibitory potential with minimum toxicity to normal human astrocytes. From the present study, it was also concluded that gossypin inhibits proliferation of U251 cells through Chk1 and Cdc25C which are cell-cycle regulatory proteins[29]. Anticarcinogenic and antitumor potential of gossypin was evaluated and showed zone of inhibition in topo I and topo II inhibition assay in *Saccharomyces cerevisiae* mutant cultures. In solid tumor harboring animals, it reduces the tumor burden and significantly inhibits the new blood vessels formation of tumor mass. Further in DMBA/croton oil induced skin papilloma model in mouse, it also reduced the papilloma formation[30]. *In vitro* cytotoxic activity of gossypin isolated from *H. vitifolius* against vero cell lines was investigated and found to be active and at 1000 mg concentration it exhibited 68.75% inhibition. In another study, gossypin inhibited NF-kappa B activation in tumor cells and this inhibitory activity of NF-kappa B activation pathway explained its importance in the suppression of carcinogenesis[23].

2.4. Analgesic activity of gossypin

Acetic acid-induced writhing model in mice was used to evaluate the analgesic activity of gossypin and found that gossypin inhibited writhing in a dose-dependent manner whereas naloxone antagonised this action. From this study we also found that the pA2 values for gossypin-naloxone and morphine-naloxone were almost same signifying the involvement of opiate receptors in the analgesic activity of gossypin[31].

2.5. Antiallergic activity of gossypin

To investigate the anti-allergic potential of gossypin, mast cell-mediated allergy model was used and result showed that gossypin inhibited antipruritics, systemic anaphylaxis reactions and further it also reduced the histamine release in rats. From these observation we can conclude that gossypin inhibit mast cell-mediated allergic reactions[32].

2.6. Antiviral activity of gossypin

The inhibitory effects of 12 flavonoids including gossypin against plaque formation of *Herpes simplex* virus type 2 (HSV-2) and 1 (HSV-1) in Vero cells was evaluated. Out of all the 12 flavonoids naringenin and hesperetin were found to be most potent against HSV-1 and HSV-2 respectively compared to all the other flavonoids including gossypin[33].

2.7. Antioxidant activity of gossypin

The antioxidant potential of gossypin was checked through *in vitro* antioxidant methods and from the result it was found that gossypin and BHT have significant antioxidant activity. Further in case of DPPH radical the value for gossypin and BHT was found to be up to 88.52% and 91.45% further justify their antioxidant potential[34]. Antioxidant activity of gossypin and some other extracts were investigated and found that gossypin had good antioxidant activity at the tested concentration[35]. In another study, gossypin also showed *in vitro* lipid peroxidation inhibitory potential[30].

2.8. Effect of gossypin on central nervous system

Maximal electroshock convulsive methods and seizures induced by pentelentetrazole, strychnine in mice were used to check the anticonvulsant potential of gossypin and result showed that gossypin significantly reduced the duration of convulsion. Further gossypin also significantly reduced the tonic extensor convulsion induced by strychnine and maximum electroshock-induced convulsions[20]. Effect of gossypin, myricitrin and naringin were tested in elevated plus maze test to know its anxiolytic activity. Result showed that in 1 mg/kg dose, both gossypin and naringin give similar effect, but in 30 mg/kg dose gossypin, it showed both sedative and anxiolytic effects. From these results we can conclude that gossypin has various CNS-mediated potential[36]. Acetic acid induced writhing assay in mice was used to know the effect of gossypin on the development of acute tolerance to morphine and results showed that gossypin pretreatment significantly attenuated the acute tolerance development which signified its potential as a substitute for morphine[37]. Effect of anti-nociceptive effect of gossypin on cholinergic and gamma amino butyric acid (GABA) neurotransmitter systems was investigated. Gossypin treatment produced an additive response which revealed the important of GABAergic and cholinergic systems in gossypin-induced anti-nociception[38].

2.9. Effect of gossypin on cardiovascular system

Effect of gossypin on cholesterol metabolism in HepG2 cells was investigated to know its cardiovascular potential and it was found that gossypin treatment reduced the total cholesterol level. Gossypin also up-regulates LDLR expression which is independent of SREBP-2 but is dependent on ERK activation[39].

2.10. Effect of gossypin on gastric system

Effect of epicatechin, hydroxyethyl rutosides and gossypin on small intestinal transit in mice was evaluated and it was found that all these compounds delayed the small intestinal transit in a dose-dependent manner. Further, yohimbine, phentolamine and naloxone were also found to be the inhibitor of the flavonoids action whereas it was not affected by hexamethonium, propranolol, prazosin, atropine, metiamide, physostigmine and pheniramine[40]. P-glycoprotein is part of a large family of efflux transporters found in the gut, gonads

and other organs. Effect of interaction of gossypin and chrysin with nitrendipine was evaluated and result showed the decreased transport rate of nitrendipine in the ileum than in the jejunum and duodenum with gossypin. Furthermore, other bioflavonoids such as gossypin, methyl hesperidin, diosmin, quercetin and chrysin also decreased the transport of nitrendipine[41].

2.11. Effect of gossypin on microorganism

Effects of gossypin isolated from *H. vitifolius* against different bacteria and fungi were tested to know their effect on microorganism and result showed that this flavone derivative revealed moderate activity against *Escherichia coli* and *Staphylococcus aureus* and mild effect against *Salmonella typhi* and *Pseudomonas aeruginosa* and showed no activity against any tested fungi[22].

2.12. Toxicity study of gossypin

Effect of gossypin at 25 or 100 mg/kg against lead toxicity was investigated for 3 week, and results found that it altered the levels of thiobarbituric acid-reactive substances, glutathione, superoxide dismutase activity and reactive oxygen species level. These alterations were significantly prevented in the gossypin treated group which signified its protective role[11]. Protective efficacy of gossypin against sulphur mustard in mice was investigated at various dose levels in various vehicles (water, PEG-300 and DMSO) with time intervals. Result showed that the gossypin given in PEG-300 has more protection against sulphur mustard toxicity than DMSO and in case of water no protection was found to be observed[21]. Effects of gossypin in oxidative stress or beta-amyloid induced toxicity in primary cultured rat cortical cells were investigated. From these results, it was found that gossypin revealed the neuroprotective effects in the cultured cortical cells which were mainly due to the inhibition of both oxidative stress and beta-amyloid induced toxicity[42]. The protective effects of various phenolic and flavonoids on the cytotoxicity of CCl_4 in rat hepatocytes were studied. Gossypin significantly inhibited alanine amine transferase release[43]. The protective effect of flavonoids in sulphur mustard induced toxicity was investigated. Administration of gossypin, vitamin E and hydroxyethyl rutosides did not alter the level of GSH but significantly reduced the MDA level, justifying the beneficial effect of flavonoids[44]. Effect of gossypin, quercetin, and flavone against sulphur mustard induced lethality was evaluated and found that protection was found to be good in case of flavonoids such as gossypin and quercetin compared to the standard tocopherol acetate. Further this study also proved that gossypin protects glutathione peroxidase significantly[45].

2.12. Effect of gossypin on other systems

Effects of flavonoids on recombinant human phosphatase of regenerating liver-3 activity were investigated by DiFMUP assay and results found that gossypin significantly inhibited recombinant PRL-3 activity. Further on the basis of the observation we can say that if number of hydroxyl group increased, inhibitory effect of flavonoids on PRL-3 would also enhance[46]. Cyclin-dependent kinase 2 (CDK2) binding effect of 347 flavonoid derivatives was docked into the crystal structure of the CDK2 in order to find flavonoids showing cyclin-dependent kinase 2 (CDK2) binding effects. The docking study showed that gossypin has a good conformational match with CDK2, which was confirmed by the binding affinity assay using NMR experiments[47]. Transient spectra and reaction rate constants of 11 flavonoids and 4 phenolic acids

were measured and results showed that some specific groups were needed in the basic skeleton for specific activity. From this study, it is concluded that C4 keto group is the active site whereas the O-dihydroxy structures in B rings are key structures for antioxidant activities of all flavonoidal compound and phenolic acids[48]. Effect of gossypin, gossypetin, bharangin and quercetin on *Escherichia coli* 46R641 cells carrying multidrug resistant TP181 plasmid were investigated and result showed that activity of all these tested compounds was found to be much higher compared to the known agents[49]. Different flavonoids and phenolic acids are tested for their ability to inhibit β -lactamase, type of inhibition and the relationship between the structure and activity. The results showed that fisetin, flavone, quercetin, catechin and gossypin are non-competitive inhibitors. Moreover it can conclude that the position of OH in the structures of molecules has a major influence[50].

3. Conclusion

Nature provides us the food material and herbal medicine for the primary healthcare and about 2–3 decades ago most of the drugs were obtained from natural sources. Different plants materials and derived products are used for the treatment of various disorders. A large number of the drugs used in the modern system of medicine are derived from natural sources. Further a large number of populations from Africa and Asian country used traditional medicines for their primary healthcare[51]. Herbal medicines are used for treatment of various ailments in the world due to the belief of its fewer side effects. Many synthetic and natural compounds have been obtained from different natural sources such as plants, minerals and organic matter[52-54]. World Health Organization (WHO) also listed many plant materials and plant product for its medicinal property[55]. Development of different food products in food science and technology cover the specific health benefits offered by food ingredients from plants including sterols, carotenoids, polyphenols and anthocyanins. Natural materials are an emerging field in food science because of their increasing popularity with consumers concerned about health[56,57]. Plant secondary metabolites are numerous and diverse; the general pathways of secondary product metabolism are conserved over a wide range of plants[58].

Flavonoids, a diverse group of phytochemicals produced by various plants are classified into eight groups: flavans, flavanones, isoflavanones, flavones, isoflavones, anthocyanidines, chalcones and flavonolignans (Figure 1). The structure of these compounds is derived from a heterocyclic hydrocarbon, chromane, by substitution of its ring C. More than 8000 flavonoidal compounds have been identified so far. Natural flavonoids usually occur as glycosides e.g. glucosides, rhamnoglucosides, and rutinoides[59]. Flavonol glycosides are located mainly in the leaves, flowers, and outer parts of plants such as skin and peel and decrease in concentration toward the central core. Fruits, vegetables, and beverages such as tea and red wine are rich sources of flavonols. Tea, onions, and apples are the most predominant food sources of flavonols in the Netherlands, Denmark, and the United States[5]. People from European countries consume up to approximately 1 g of different flavonoids per day in the common diet, depending on the food source. Flavonoids have been reported to exert multiple biologic effects including antiinflammatory, antiallergic, antiviral, anticancer activities etc.[13].

Conflict of interest statement

We declare that we have no conflict of interest.

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References

- [1] Tripoli E, Guardia ML, Giammanco S, Majo DD, Giammanco M. Citrus flavonoids: molecular structure, biological activity and nutritional properties: a review. *Food Chem* 2007; **104**: 466-79.
- [2] de Souza Dos Santos MC, Gonçalves CF, Vaisman M, Ferreira AC, de Carvalho DP. Impact of flavonoids on thyroid function. *Food Chem Toxicol* 2011; **49**: 2495-502.
- [3] Karioti A, Bilia AR, Skaltsa H. *Quercus ilex* L.: a rich source of polyacylated flavonoid glucosides. *Food Chem* 2010; **123**: 131-42.
- [4] Trichopoulou A, Vasilopoulou E, Hollman P, Chamalides CH, Foufa E, Kaloudis TR, et al. Nutritional composition and avonoid content of edible wild greens and green pies: a potential rich source of antioxidant nutrients in the Mediterranean diet. *Food Chem* 2000; **70**: 319-23.
- [5] Aherne SA, O'Brien NM. Dietary flavonols: chemistry, food content, and metabolism. *Nutrition* 2002; **18**: 75-81.
- [6] Williams RJ, Spencer JP. Flavonoids, cognition, and dementia: actions, mechanisms, and potential therapeutic utility for Alzheimer disease. *Free Radic Biol Med* 2012; **52**: 35-45.
- [7] Cook NC, Samman S. Flavonoids-chemistry, metabolism, cardioprotective effects, and dietary sources. *J Nutr Biochem* 1996; **7**: 66-76.
- [8] Heim KE, Tagliaferro AR, Bobilya DJ. Flavonoid antioxidants: chemistry, metabolism and structure-activity relationships. *J Nutr Biochem* 2002; **13**: 572-84.
- [9] Erlund I. Review of the flavonoids quercetin, hesperetin, and naringenin. Dietary sources, bioactivities, bioavailability, and epidemiology. *Nutr Res* 2004; **24**: 851-74.
- [10] Thamizhinyan V, Vijayaraghavan K, Subramanian SP. Gossypin, a flavonol glucoside protects pancreatic beta-cells from glucotoxicity in streptozotocin-induced experimental diabetes in rats. *Biomed Prev Nutr* 2012; **2(4)**: 239-45.
- [11] Gautam P, Flora SJ. Oral supplementation of gossypin during lead exposure protects alteration in heme synthesis pathway and brain oxidative stress in rats. *Nutrition* 2010; **26**: 563-70.
- [12] Yang B, Halttunen T, Raimo O, Price K, Kallio H. Flavonol glycosides in wild and cultivated berries of three major subspecies of *Hippophaë rhamnoides* and changes during harvesting period. *Food Chem* 2009; **115**: 657-64.
- [13] Rusak G, Gutzeit HO, Mqller JL. Structurally related flavonoids with antioxidative properties differentially affect cell cycle progression and apoptosis of human acute leukemia cells. *Nutr Res* 2005; **25**: 141-53.
- [14] Fernández SP, Wasowski C, Loscalzo LM, Granger RE, Johnston GA, Paladini AC, et al. Central nervous system depressant action of flavonoid glycosides. *Eur J Pharmacol* 2006; **539**: 168-76.
- [15] Kim JD, Liu L, Guo W, Meydani M. Chemical structure of flavonols in relation to modulation of angiogenesis and immune-endothelial cell adhesion. *J Nutr Biochem* 2006; **17**: 165-76.
- [16] Castillo-Muñoz N, Gómez-Alonso S, García-Romero E, Hermosín-Gutiérrez I. Flavonol profiles of *Vitis vinifera* white grape cultivars. *J Food Comp Anal* 2010; **23**: 699-705.
- [17] Makrisa DP, Kallithraka S, Kefalas P. Flavonols in grapes, grape products and wines: burden, profile and influential parameters. *J Food Comp Anal* 2006; **19**: 396-404.
- [18] Merzlyak MN, Solovchenko AE, Smagin AI, Gitelson AA. Apple flavonols during fruit adaptation to solar radiation: spectral features and technique for non-destructive assessment. *J Plant Physiol* 2005; **162**: 151-60.

- [19] Vrhovsek U, Masuero D, Palmieri L, Mattivi F. Identification and quantification of flavonol glycosides in cultivated blueberry cultivars. *J Food Comp Anal* 2012; **25**: 9-16.
- [20] Rasilingam D, Duraisamy S, Subramanian R. Anticonvulsant activity of bioflavonoid gossypin. *Bangladesh J Pharmacol* 2009; **4**: 51-4.
- [21] Gautam A, Vijayaraghavan R. Prophylactic effect of gossypin against percutaneously administered sulfur mustard. *Biomed Environ Sci* 2007; **20**: 250-9.
- [22] Chamundeeswari D, Sukumar E, Amar K, Reddy NB, Kumar IA, Chowdry BV, et al. Cytotoxic and antibacterial activities of gossypin. *Nat Prod Sci* 2007; **13**: 300-3.
- [23] Kunnumakkara AB, Nair AS, Ahn KS, Pandey MK, Yi Z, Liu M, et al. Gossypin, a pentahydroxy glucosyl flavone, inhibits the transforming growth factor beta-activated kinase-1-mediated NF-kappaB activation pathway, leading to potentiation of apoptosis, suppression of invasion, and abrogation of osteoclastogenesis. *Blood* 2007; **109**: 5112-21.
- [24] Venkatesan T, Sorimuthu Pillai S. Antidiabetic activity of gossypin, a pentahydroxyflavone glucoside, in streptozotocin-induced experimental diabetes in rats. *J Diabetes* 2012; **4**: 41-6.
- [25] Chen CH, Hsu HJ, Huang YJ, Lin CJ. Interaction of flavonoids and intestinal facilitated glucose transporters. *Planta Med* 2007; **73**: 348-54.
- [26] Mada SR, Metukuri MR, Burugula L, Reddanna P, Krishna DR. Antiinflammatory and antinociceptive activities of gossypin and procumbentin--cyclooxygenase-2 (COX-2) inhibition studies. *Phytother Res* 2009; **23**: 878-84.
- [27] Ferrándiz ML, Alcaraz MJ. Anti-inflammatory activity and inhibition of arachidonic acid metabolism by flavonoids. *Agents Actions* 1991; **32**: 283-8.
- [28] Ferrándiz ML, Nair AG, Alcaraz MJ. Inhibition of sheep platelet arachidonate metabolism by flavonoids from Spanish and Indian medicinal herbs. *Pharmazie* 1990; **45**: 206-8.
- [29] Shi L, Chen J, Wang YY, Sun G, Liu JN, Zhang JX, et al. Gossypin induces G2/M arrest in human malignant glioma U251 cells by the activation of Chk1/Cdc25C pathway. *Cell Mol Neurobiol* 2012; **32**: 289-96.
- [30] Babu BH, Jayram HN, Nair MG, Ajaikumar KB, Padikkala J. Free radical scavenging, antitumor and anticarcinogenic activity of gossypin. *J Exp Clin Cancer Res* 2003; **22**: 581-9.
- [31] Viswanathan S, Sambantham PT, Reddy K, Kameswaran L. Gossypin-induced analgesia in mice. *Eur J Pharmacol* 1984; **98**: 289-91.
- [32] Ganapaty S, Chandrashekhar VM, Narsu ML. Evaluation of anti-allergic activity of gossypin and suramin in mast cell-mediated allergy model. *Indian J Biochem Biophys* 2010; **47**: 90-5.
- [33] Lee J, Kim Y, Lee C, Lee H, Han S. Antiviral activity of some flavonoids on herpes simplex viruses. *Korean J Pharmacogn* 1999; **30**: 34-9.
- [34] Ganapaty S, Chandrashekhar VM, Chitme HR, Narsu ML. Free radical scavenging activity of gossypin and nevadensin: an *in-vitro* evaluation. *Indian J Pharmacol* 2007; **39**: 281-3.
- [35] Rajnarayana K, Ajitha M, Gopireddy G, Giriprasad VS. Comparative antioxidant potential of some fruits and vegetables using DPPH method. *Int J Pharm Technol* 2011; **3**: 1952-7.
- [36] Fernandez SP, Nguyen M, Yow TT, Chu C, Johnston GA, Hanrahan JR, et al. The flavonoid glycosides, myricitrin, gossypin and naringin exert anxiolytic action in mice. *Neurochem Res* 2009; **34**: 1867-75.
- [37] Ramaswamy S, Viswanathan S. Influence of gossypin on the development of acute tolerance to morphine induced antinociception. *Indian J Exp Biol* 1997; **35**: 413-4.
- [38] Viswanathan S, Thirugnanasambantham P, Ramaswamy S, Bapna JS. A study on the role of cholinergic and gamma amino butyric acid systems in the anti-nociceptive effect of gossypin. *Clin Exp Pharmacol Physiol* 1993; **20**: 193-6.
- [39] Lu N, Li Y, Qin H, Zhang YL, Sun CH. Gossypin up-regulates LDL receptor through activation of ERK pathway: a signaling mechanism for the hypocholesterolemic effect. *J Agric Food Chem* 2008; **56**: 11526-32.
- [40] Viswanathan S, Thirugnana Sambantham P, Bapna JS, Kameswaran L. Flavonoid-induced delay in the small intestinal transit: possible mechanism of action. *Arch Int Pharmacodyn Ther* 1984; **270**: 151-7.
- [41] Rajnarayana K, Venkatesham A, Krishna DR. Influence of some bioflavonoids on the transport of nitrendipine. *Drug Metabol Drug Interact* 2008; **23**: 299-310.
- [42] Yoon I, Lee KH, Cho J. Gossypin protects primary cultured rat cortical cells from oxidative stress- and beta-amyloid-induced toxicity. *Arch Pharm Res* 2004; **27**: 454-9.
- [43] Añón MT, Ubeda A, Alcaraz MJ. Protective effects of phenolic compounds on CCl₄-induced toxicity in isolated rat hepatocytes. *Z Naturforsch C* 1992; **47**: 275-9.
- [44] Vijayaraghavan R, Sugendran K, Pant SC, Husain K, Malhotra RC. Dermal intoxication of mice with bis(2-chloroethyl)sulphide and the protective effect of flavonoids. *Toxicology* 1991; **69**: 35-42.
- [45] Vijayaraghavan R, Gautam A, Sharma M, Satish HT, Pant SC, Ganesan K. Comparative evaluation of some flavonoids and tocopherol acetate against the systemic toxicity induced by sulphur mustard. *Indian J Pharmacol* 2008; **40**: 114-20.
- [46] He TP, Liang NC, Lin XC, Liu W. Effect of seven kinds of flavonoids on recombinant human protein tyrosine phosphatase. *Zhong Yao Cai* 2010; **33**: 771-4.
- [47] Kim H, Lee E, Kim J, Jung B, Chong Y, Ahn JH, et al. A flavonoid gossypin binds to cyclin-dependent kinase 2. *Bioorg Med Chem Lett* 2008; **18**: 661-4.
- [48] Cai Z, Li X, Katsumura Y. Interaction of hydrated electron with dietary flavonoids and phenolic acids: rate constants and transient spectra studied by pulse radiolysis. *Free Radic Biol Med* 1999; **27**: 822-9.
- [49] Lakshmi VV, Sridhar P, Polasa H. Loss of plasmid linked antibiotic resistance in *Escherichia coli* on treatment with some phenolic compounds. *FEMS Microbiol Lett* 1989; **48**: 275-8.
- [50] Naoual B, Djalal M, Abderrahmane B. Kinetic study of different flavonoids as inhibitors of beta-lactamase enzyme. *Afr J Biochem Res* 2011; **5**: 321-7.
- [51] Patel K, Tahilyani V, Gadewar M, Patel DK. A review on pharmacological and analytical aspects of diosmetin – a concise report. *Chin J Integr Med* 2013; **19**(10): 792-800.
- [52] Patel DK, Kumar R, Prasad SK, Hemalatha S. Pharmacologically screened aphrodisiac plant – a review of current scientific literature. *Asian Pac J Trop Biomed* 2011; (Suppl 1): S131-8.
- [53] Patel DK, Lalloo D, Kumar R, Hemalatha S. *Pedalium murex* Linn – an overview of its phytopharmacological aspects. *Asian Pac J Trop Med* 2011; **4**: 748-55.
- [54] Patel DK, Prasad SK, Kumar R, Hemalatha S. Cataract: a major secondary complication of diabetes, its epidemiology and an overview on major medicinal plants screened for anticataract activity. *Asian Pac J Trop Dis* 2011; **1**(4): 323-9.
- [55] Patel DK, Prasad SK, Kumar R, Hemalatha S. An overview on antidiabetic medicinal plants having insulin mimetics property. *Asian Pac J Trop Biomed* 2012; **2**: 320-30.
- [56] Ávila Ma, Hidalgo M, Sánchez-Moreno C, Pelaez C, Requena T, de Pascual-Teresa S. Bioconversion of anthocyanin glycosides by *Bifidobacteria* and *Lactobacillus*. *Food Res Int* 2009; **42**: 1453-61.
- [57] Ko M, Cheigh C, Cho S, Chung M. Subcritical water extraction of flavonol quercetin from onion skin. *J Food Eng* 2011; **102**: 327-33.
- [58] Graham TL. Flavonoid and flavonol glycoside metabolism in *Arabidopsis*. *Plant Physiol Biochem* 1998; **36**: 135-44.
- [59] Hodek P, Trefil P, Stiborová M. Flavonoids-potent and versatile biologically active compounds interacting with cytochromes P450. *Chem Biol Interact* 2002; **139**: 1-21.