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New Understandings of Flavonoids' Pharmacology

Dr. Shaktibala Dutta[1]*, Dr. Jyotsna Sharma[2], Dr. Vaishali Lote[3]

[1] Professor, Department of Pharmacology, Santosh Medical College and Hospital, Santosh Deemed to be University, Ghaziabad, India

[2] Professor, Department of Pharmacology, Santosh Medical College and Hospital, Santosh Deemed to be University, Ghaziabad, India

[3] Assistant Professor, Department of Pharmacology, Santosh Medical College and Hospital, Santosh Deemed to be University, Ghaziabad, India

ABSTRACT:

Flavonoids are widely dispersed secondary metabolites that are currently present in high concentrations in the average person's diet. The most recent data, the majority of which have been published in Phytotherapy Research, are highlighted in this article along with some of the most recent advancements in the pharmacology of flavonoids and related polyphenolic compounds. These data highlight new flavonoid anti-inflammatory, antilipidemic, antihyperglycemic, antiviral, hepatoprotective, gastric antiulcer, cardioprotective, neuroprotective, antioxidant, and anticancer actions. These latest findings support the perspective for a therapeutic use and support the various positive pharmacological activities that have long been recognised.

Keywords*:* apoptosis; cancer; flavonoids; antioxidant; isoflavonoids; phytoestrogens; quercetin; silybin

INTRODUCTION:

Low molecular weight phenolic chemicals known as flavonoids are secondary metabolites that can be found in tea, red wine, fruits, vegetables, nuts, seeds, herbs, and stems and flowers (Middleton et al., 2000). Both in their free form and as glycosides, flavonoids have a number of significant pharmacological effects that may be of clinical importance (Di Carlo et al., 1999; Samuelsson, 1999). Flavonoids can be categorised structurally based on the presence of various substituents on the rings and the level of benzo-g-pyrone saturation. The flavones, flavanones, and flavonols are the most prevalent classes. The isoflavonoids are created when the B-ring is moved to carbon 2 of the three-carbon chain.

Flavonolignans are substances that are derived from the flavanol taxiflorin (2,3-dihydroquercetin) and coniferyl alcohol, such as silybin, which is the primary ingredient of the complex silymarin and is available as an extract from the fruit of the milk thistle Silybum marianum (Abenavoli et al., 2010). The Hungarian biologist Albert Szent-Gyorgyii, who won the Nobel Prize in Physiology or Medicine in 1937, reported the usefulness of citrus peel flavonoids in avoiding capillary bleeding and fragility linked to scurvy as the first proof of a biological action of flavonoids in 1938. (Samuelsson, 1999).

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Since then, flavonoids have been linked to a wide range of biological effects (Prasad et al., 2010, Amado et al., 2011, Hanrahan et al., Procházková et al., 2011, Dajas, 2012). With a focus on information very recently published in Phytotherapy Research, we discuss some of the most recent advancements in the pharmacology of flavonoids in this article.

Central nervous system

According to studies by Choudhary et al. (2011), Guo et al. (2011), Herrera-Ruiz et al. (2011), Jäger and Saaby (2011), Jiang et al. (2011), Fernandez et al. (2012), Karim et al. (2012), and Zhou et al. (2012), flavonoids have the ability to affect central nervous system activity (CNS) through binding to the benzodiazepine site on the

Recent research reported in the journal Phytotherapy Research has demonstrated that flavonoids can affect CNS function and mood. In particular, I chronic oral administration of hesperidin resulted in anxiolytic-like effects (Wasowski et al., 2012); (ii) cyanidin-3-glucoside improved short-term spatial recognition memory disturbance in the Y-maze test (Can and Ozkay, 2012); and (iii) Hypericum montbretti extract, in which rutin and quercitrin were identified as the major phenolic compounds (Can and Ozkay, 2012).

Through a variety of biological mechanisms, including the reduction of oxidative stress, excitotoxicity, and apoptotic neuronal death, as well as the regulation of the kinase signal cascade, flavonoids have been shown to have neuroprotective effects on cells and animal models (Campos-Esparza Mdel and Torres-Ramos, 2010; Gutierrez-Merino et al., 2011; Hanrahan et al. Numerous flavonoids, notably those newly identified from Peltiphyllum peltatum or Sophora flavescens (Habtemariam and Cowley, 2012; Jung et al., 2011), have been demonstrated to be inhibitors of the enzyme acetylcholinesterase, a crucial target for the treatment of Alzheimer's disease. Additionally, flavonoids suppress neuroinflammatory processes that play a role in the aetiology of neurodegenerative diseases (Spencer et al., 2012). For instance, Lim and colleagues demonstrated that lipopolysaccharide-induced microglial activation and the generation of proinflammatory mediators were inhibited by methylalpinumisoflavone extracted from Cudrania tricuspidata via reducing NF-kB signalling and the phosphorylation of MAPKs (Lim et al., 2012).

Baicalein, a flavonoid produced from Scutellaria baicalensis, has been shown to support cognitive behaviour and to prevent damage to neural cells (Wang et al., 2011). Baicalein reduced brain infarction after focal brain ischemia, according to several investigations (Jin et al., 2008; Pallast et al., 2010). Baicalein has recently been demonstrated to have the ability to lessen the neuronal damage caused in the hippocampus of mice that have experienced temporary global brain ischemia. The authors postulated that baicalein's ability to prevent global ischemia is at least partially a result of its ability to decrease MMP-9 activity (Lee and Lee, 2012).

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Cardiovascular system

For the treatment of cardiovascular disorders, flavonoids and related polyphenolic substances are of great interest (Hooper et al., 2012). In addition to their antioxidant properties, flavonoids may control many signalling pathways that contribute to the development of cardiovascular disorders (Wallace, 2011). Importantly, in diseases like hypertension, stroke, or the metabolic syndrome, flavonoids increase endothelial nitric oxide (NO) production, which causes endothelium-dependent relaxation (Andriantsitohaina et al., 2012). Cohort studies and randomised trials have provided evidence that diets high in flavonoids may have positive impacts on cardiovascular health, although larger epidemiological studies and long-term randomised trials are still needed to corroborate these results (van Dam et al., 2013).

The positive effects of flavonoids in cardiovascular illnesses have been verified by recent preclinical research, which was published in Phytotherapy Research. For instance, Kraussianone-2, a pyrano-isoflavone isolated from the roots of Eriosema kraussianum, improved foetal outcomes and decreased antiangiogenic factors in pregnant rats (Ramesar et al., 2012); (ii) hesperidin, glucosyl hesperidin, a water-soluble flavonoid, has been shown to protect H9c2 cardiomyocytes against oxidative stress (Bijak et al., 2013). Last but not least, research on hypertensive individuals revealed that ()-epicatechin exerted protective benefits against oxidative stress brought on by tert-butyl hydroperoxide on isolated erythrocytes (Kumar et al., 2012).

Dyslipidemia and obesity

By inhibiting hepatic fatty acid production and increasing fatty acid oxidation, flavonoids protect against experimental hepatic steatosis, dyslipidemia, and insulin sensitivity (Cherniack, 2011; Assini et al., 2013). Recently studied flavonoids and isoflavonoids include quercetin, isoquercitrin, morelloflavone, biochanin A, and formononetin. Quercetin, which has been linked to a decreased risk of cardiovascular disease (Russo et al., 2012), significantly increased the expression of the gene for low density lipoprotein (LDL) receptor in hepatic cells, which may have the effect of causing hypolipidemic effects by enhancing the removal of circulating LDL cholesterol from the blood (Moon et al., 2012). By inhibiting Wnt/b-catenin signalling, the compound isoquercitrin from Persicaria hydropiper reduced adipogenesis in adipocytes (Lee et al., 2011a, 2011b). Morelloflavone, a biflavonoid from Garcinia dulcis, inhibited HMG-CoA reductase, the rate-limiting enzyme of cholesterol manufacture (Hutadilok-Towatana et al., 2007), which is known to have hypocholesterolemic action (Tuansulong et al., 2011).

Red clover (Trifolium pratense) formononetin and biochanin A improved the lipid profiles of diabetic mice, with this improvement at least partially attributed to the activation of hepatic peroxisome proliferator-activated receptor a. (Qiu et al., 2012).

Additionally to isolated substances, flavonoid-rich plant extracts have been shown to have hypolipidemic effects (Capasso et al., 2003; An et al., 2011).

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In line with this, it has been demonstrated that adipokine expression in the mesenteric fat of diet-induced obese mice is affected by the addition of a quercetin-rich onion peel extract (Kim et al., 2012f). Additionally, primary adipocytes' lipolysis was decreased by oligonol, a standardised formulation made up of 18.6% proanthocyanidin dimers and trimers and 17.6% catechin-type monomers from grape seeds or lychee fruit. Oligonol's lipolytic action was accompanied by a noticeably higher level of extracellular signalling-related kinase 1/2 activation (Ogasawara et al., 2011).

Diabetes

Numerous flavonoids have been shown to have biological effects on type 2 diabetes mellitus biological targets such a-glycosidase, glucose cotransporter, or aldose reductase. Flavonoids also enhance glucose metabolism and consumption while acting as antioxidants to protect against the harmful effects of hyperglycemia (Nicolle et al., 2011; Qi et al., 2011; Tang et al., 2011; Zheng et al., 2011). According to these hypotheses, it has recently been demonstrated that flavonoids from the date palm Phoenix dactylifera and Boldoa purpurascens have antihyperglycemic activity in the animal type of diabetes brought on by alloxan (González Mosquera et al., 2013; Michael et al., 2013). Additionally, flavonoids have positive benefits on problems linked to diabetes. Thus, in macrophages activated by high glucose, the isoflavonoid glabridin from licorice root increased manganese superoxide dismutase, catalase, and paraoxonase 2. (Yehuda et al., 2011). These findings imply that glabridin may boost antioxidant defence systems and act as an antiatherogenic agent in diabetes.

Inflammation and immune system

Flavonoids have a surprising variety of biochemical and pharmacological behaviours that point to immune system and anti-inflammatory benefits (Middleton et al., 2000). The in vivo anti-inflammatory effects of flavonoids have been explained by a number of different modes of action. These include antioxidant action, inhibition of enzymes that produce eicosanoids, a decrease in the generation of proinflammatory chemicals, and modification of the expression of proinflammatory genes (Garca-Lafuente et al., 2009). Additionally, inflammatory cells like lymphocytes, natural killer cells, monocytes, neutrophils, mast cells, and macrophages have their functions modulated by flavonoids (Middleton et al., 2000).

Li and associates discovered recently that the flavonol icariin, the primary component of the Chinese plant Herba epimedii, which has immunomodulatory and antirheumatic properties, stimulated the expression (and its mRNA) of toll-like receptor 9 in murine macrophages (Li et al., 2011). Icariin also altered the levels of several immune response-related markers, including interleukin-6, tumour necrosis factor-a, and myeloid differentiation factor 88. Another intriguing study discovered quercetin blocked the complement classical pathway (Moon et al., 2011), which is important for autoimmune illnesses and for the defence against infections. Finally, 20 young male long-distance runners participated in a clinical experiment to examine the impact of a flavanol-rich lychee fruit extract (FRLFE) on inflammation and tissue damage. The blood interleukin6 level changed substantially less between pre- and mid-

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training in the FRLFE group compared to the placebo group, but the serum transforming growth factor-b level changed significantly more between pre- and post-training in the FRLFE group. The authors draw the conclusion that taking FRLFE supplements may reduce tissue damage or inflammation brought on by high-intensity exercise training (Nishizawa et al., 2011). An experimental investigation discovered that certain flavonoids extracted from Citrus aurantium have anti-inflammatory properties in L6 skeletal muscle cells, supporting this clinical trial (Kim et al., 2012a).

Cancer

A variety of methods, including carcinogen inactivation, antiproliferation, cell cycle arrest, induction of apoptosis, suppression of angiogenesis, antioxidation, and reversal of multidrug resistance, are used by flavonoids to fight cancer (Gibellini et al., 2011; Chahar et al., 2012). According to epidemiological research, eating foods high in flavonoids may lower your chance of developing breast, colon, lung, prostate, and pancreatic cancer. Inconclusive relationships have been identified by certain studies, nevertheless (Romagnolo and Selmin, 2012). Numerous flavonoids, including quercetin (Yang et al., 2011), rutin (Marrassini et al., 2011), hesperetin (Aranganathan and Nalini, 2012), xanthohumol (Zajc et al., 2012), silymarin (Yu et al., 2012), chrysoplenetin and chrysosplenol D (Additional research has demonstrated that liquiritigenin, a flavanone present in many plants including licorice, promoted apoptosis in HeLa cells, an effect linked to the up-regulation of p53 and Bax, the down-regulation of Bcl-2 and surviving, the release of cytochrome c, and increased activity of caspase-9 and -3. (Liu et al., 2011).

Respiratory tract

Flavonoids have beneficial effects on respiratory tract conditions such as anti-inflammatory (Rogerio et al., 2010; Choi et al., 2012b; Huang and Liou, 2012), anti-allergic (Kulka, 2009; Li et al., 2010), antioxidant (Guabiraba et al., 2010a, 2010b; Gomes et al., 2012; Li et al., 2012; Yan et al., 2011) According to Kim et al. (2012)b and Yang et al. (2012), flavonoids also control airway mucus secretion, which is crucial for the body's defence against harmful microorganisms. A number of flavonoids and related compounds have recently been demonstrated to be able to decrease the formation of mucin, which is a key factor in regulating the physicochemical characteristics of airway mucus, according to certain research recently published in Phytotherapy Research. According to research done by Kim et al. (2012c, 2012e), MUC5AC mucin gene expression as well as the associated production and secretion of mucin in airway epithelial cells are inhibited by silibinin, apigenin, wogonin, and prunetin.

Digestive tract

Flavonoids reduce the contraction and motility of the gut. and diarrhoea (Gálvez et al., 1993; Di Carlo et al., 1993). Gharzouli and Holzer (2004), Capasso et al. (2008), and 1995 reduce visceral pain (Gadotti; Borrelli et al., 2012) intestinal inflammation (Shi et al., 2012; et al., 2005) (Park et al., 2012; Ocete et al., 1998), and exert Hepatoprotective (Kim et al., 2011b;

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Jayaraj et al., 2007) gastrointestinal antiulcer effects (Di Carlo; Liu et al., 2012) Izzo et al., 1994; Suzuki et al., 1998; Borrelli; et al., 1994; as well as Izzo (2000) and Hariprasath et al. (2012). Concerning the action of gastric ulcers, Awad and colleagues demonstrated that four flavonoids from Euphorbia identified as naringenin, aromadendrin, and cuneata the compounds apigenin and 4'-O-methoxy-luteolin-7-O-rhamnoglucoside, ethanol model that showed antiulcerogenic activity stomach ulcer (Awaad et al., 2013). Additionally, additional Hypericum erectum flavonoids decreased the Helicobacter pylori expansion, a significant contributing factor to stomach ulcer. Finally, a fascinating investigation by Bulgari and associates discovered that chamomile had anti-inflammatory activity in human gastric cancer cells, an outcome attributed to gastric and neutrophil elastase inhibition Secretion and action of metalloproteinase-9. Flavonoid-7- The primary components of chamomile flowers, glycosides, may be in charge of the anti-inflammatory effects (Bulgari) et al., 2012).

Genitourinary tract and reproduction

Patients with prostatitis, UTIs, and other genitourinary conditions frequently take flavonoid-rich herbal remedies (Katz, 2002; Theoharides, 2007; Côté et al., 2010). In isolated bladder, vas deferens, and uterus preparations, flavonoids also have antispasmodic effects (Rojas et al., 1996; Capasso and Mascolo, 2003; Capasso et al., 2004; Capasso et al., 2005; Capasso et al., 2006; Macêdo et al., 2011). According to a recent study, the flavonoid isoliquiritigenin, which was isolated from the roots of Glycyrrhiza glabra, not only reduces acetic acid-induced writhing, an experimental model of visceral pain, but also has a spasmolytic impact on uterine contractions, which is related to Ca2+ channels (Shi et al., 2012).

For the treatment of postmenopausal osteoporosis, a number of prescription medications are available; the majority of these contain isoflavones, which are known to have estrogenic effects (Al-Anazi et al., 2011; Swarnkar et al., 2012). Recent studies have demonstrated that isoflavones help reduce the symptoms of experimental menopause. For instance, Cho and Jun (2012) showed that isoflavones from Pueraria lobata prevented the loss of bone mineral density in the femurs of mice during ovariectomies. Two isoflavones from the African medicinal plant Erythrina lysistemon, alpinumisoflavone and abyssinone V-4'-methyl, were discovered in another investigation to have estrogenic effects on the female rat reproductive system and in cell culture (Mvondo et al., 2012). Finally, oral administration of an isoflavone methanol extract from Trifolum pratenses demonstrated analgesic effects in ovariectomized rats as demonstrated by the decrease in pain threshold observed utilising tail flicking and formalin tests (Vishali et al., 2011). Systematic evaluations have also shown that isoflavones are effective in treating diseases and symptoms related to menopause (Borrelli and Ernst, 2010).

In isolated cells and animals, the isoflavone genistein can lessen radiation-induced experimental toxicity (Nambiar et al., 2011). However, little is known about its impact on a potential radioprotective action against radiation-induced testicular damage. A recent study showed that genistein improved several spermatogenesis-related factors in mice given pelvic

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radiation, and this benefit was linked to a notable reduction in the generation of radiation-induced ROS (Kim et al., 2012d).

Dermatology

Flavonoids are multi-functional substances that are largely employed in dermatology for their blood vessel-dilating, anti-inflammatory, and calming effects (Arct and Pytkowska, 2008). In HaCaT cells, an immortalised human adult keratinocyte cell line, Moon and Kim discovered that hesperidin inhibited the inflammatory response brought on by NaOH peroxide via modulating the NF-kB/IkBa and p38 MAPK pathways and by lowering the production of proinflammatory cytokines. The findings imply that hesperidin-rich plants may play a part in the management of inflammatory skin illnesses brought on by UV radiation (Moon & Kim, 2012). Another study discovered that the ortho-dihydroxyisoflavone derivatives 8'- and 3'-hydroxydaidzein from fermented Korean soybean paste inhibited melanin formation in B16 melanoma cells similarly to treatment with kojic acid, a known bleaching agent. The RT-PCR results showed that the hydroxydaidzeins were responsible for transcriptional inhibition of many melanogenesis genes, which led to depigmentation (Goh et al., 2012).

Antimicrobial and antiparasitic activities

The majority of flavonoids, particularly those that are isoflavones and prenylated flavonoids, are regarded as constitutive antibacterial components (Mukne et al., 2011). Many academic institutions have worked to clarify the antibacterial modes of action of certain flavonoids. For instance, quercetin's activity has been at least partially linked to DNA gyrase inhibition (Cushnie and Lamb, 2006). A number of recent studies published in Phytotherapy Research have shown that flavonoids extracted from plants like Larrea tridentate, Erythrina caffra, and Melampyrum arvense have antiviral (Alvarez et al., 2012; Choi et al., 2012a), antibacterial (Chukwujekwu et al., 2011; Favela-Hernández et al., 2012 Interestingly, Choi and colleagues demonstrated that quercetin 3-rhamnoside, when administered orally, reduced mortality in mice infected with the influenza A/WS/33 virus. This effect was connected to a delay in the onset or progression of pulmonary histological lesions (Choi et al., 2012a). Quercetin 3-rhamnoside "may be an appealing lead for the development of antiviral medicines against influenza virus," the authors write in their conclusion.

Herb–drug interactions

Flavonoids have the potential to alter the expression of cytochrome P450 (CYP) enzymes and/or P-glycoprotein, which are crucial in the pharmacokinetic interactions between herbs and drugs (Borrelli and Izzo, 2009; Gurley et al., 2012; Izzo, 2012). Recently, it has been demonstrated that quercetin, a low affinity ligand of the transcription factor AhR, which controls the development of the CYP 1A enzymes, induces the expression of AhR and CYP1A1 in hepatic (HepG2) cells (Vrba et al., 2012).

Scutellarin, the most significant flavone glycoside in Erigeron breviscapus, was discovered in a different study to enhance plasma concentrations of phenacetin and directly block CYP1A2, an enzyme involved in phenacetin metabolism (Jian et al., 2012). Finally, it was shown that

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the isoflavone biochanin A decreased the bioavailability of the drug tamoxifen and its metabolite 4-hydroxytamoxifen in rats (Singh et al., 2012). Tamoxifen is a substrate of P-glycoprotein and cytochrome 3A. Together, these findings offer fresh perspectives on the part flavonoids play in the interactions between herbs and medications.

CONCLUSION:

Recent experimental and human studies, including those in this article that were published in Phytotherapy Research, as well as similar studies that were published in other journals over the previous two years, have confirmed that flavonoids have an impact on a number of critically important mechanisms involved in a wide range of diseases, including cancer, neurodegenerative diseases, diabetes, obesity, and related dyslipidemia, as well as cardiovascular, respiratory, dermatological, and digestive disorders. To completely develop this class of plant-derived chemicals as medicinal medicines, however, requires further funding from both academia and business. Sadly, it is challenging to conduct carefully planned clinical studies, possibly because there is little intellectual property protection.

REFERENCE:

1. Abenavoli L, Capasso R, Milic N, Capasso F. 2010. Milk thistle in liver diseases: past, present, future. Phytother Res 24(10): 1423–1432.
2. Al-Anazi AF, Qureshi VF, Javaid K, Qureshi S. 2011. Preventive effects of phytoestrogens against postmenopausal osteoporosis as compared to the available therapeutic choices: An overview. J Nat Sci Biol Med 2(2): 154–163.
3. Alvarez AL, Dalton KP, Nicieza I et al. 2012. Bioactivity-guided fractionation of Phyllanthus orbicularis and identification of the principal anti HSV-2 compounds. Phytother Res 26(10): 1513–1520.
4. Amado NG, Fonseca BF, Cerqueira DM, Neto VM, Abreu JG. 2011. Flavonoids: potential Wnt/beta-catenin signaling modulators in cancer. Life Sci 89(15–16): 545–554.
5. An Y, Zhang Y, Li C, Qian Q, He W, Wang T. 2011. Inhibitory effects of flavonoids from Abelmoschus manihot flowers on triglyceride accumulation in 3T3-L1 adipocytes. Fitoterapia 82(4): 595–600.
6. Andriantsitohaina R, Auger C, Chataigneau T et al. 2012. Molecular mechanisms of the cardiovascular protective effects of polyphenols. Br J Nutr 108(9): 1532–1549.
7. Aranganathan S, Nalini N. 2012. Antiproliferative Efficacy of Hesperetin (Citrus Flavanoid) in 1,2-DimethylhydrazineInduced Colon Cancer. Phytother Res. doi:10.1002/ptr.4826
8. Arct J, Pytkowska K. 2008. Flavonoids as components of biologically active cosmeceuticals. Clin Dermatol 26(4): 347–357.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper **© 2012 IJFANS. All Rights Reserved, UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4 ,2022**

9. Argyropoulou A, Samara P, Tsitsilonis O, Skaltsa H. 2012. Polar constituents of Marrubium thessalum Boiss. & Heldr. (Lamiaceae) and their cytotoxic/cytostatic activity. Phytother Res 26(12): 1800–1806.

10. Assini JM, Mulvihill EE, Huff MW. 2013. Citrus flavonoids and lipid metabolism. Curr Opin Lipidol 24(1): 34–40.

11. Aviello G, Canadanovic-Brunet JM, Milic N et al. 2011. Potent antioxidant and genoprotective effects of boeravinone G, a rotenoid isolated from Boerhaavia diffusa. PLoS One 6(5): e19628.

12. Aviello G, Rowland I, Gill CI et al. 2010. Anti-proliferative effect of rhein, an anthraquinone isolated from Cassia species, on Caco-2 human adenocarcinoma cells. J Cell Mol Med 14(7): 2006–2014.

13. Awaad AS, Al-Jaber NA, Moses JE, El-Meligy RM, Zain ME. 2013. Antiulcerogenic activities of the extracts and isolated flavonoids of Euphorbia cuneata Vahl. Phytother Res 27(1): 126–130.

14. Awale S, Linn TZ, Li F et al. 2011. Identification of chrysoplenetin from Vitex negundo as a potential cytotoxic agent against PANC-1 and a panel of 39 human cancer cell lines (JFCR39). Phytother Res 25(12): 1770–1775.

15. Bijak M, Saluk J, Ponczek MB, Nowak P. 2013. Antithrombin effect of polyphenol-rich extracts from black chokeberry and grape seeds. Phytother Res 27(1): 71–76.

16. Borrelli F, Ernst E. 2010. Alternative and complementary therapies for the menopause. Maturitas 66(4): 333–343.

17. Borrelli F, Izzo AA. 2000. The plant kingdom as a source of antiulcer remedies. Phytother Res 14(8): 581–591.

18. Borrelli F, Izzo AA. 2009. Herb-drug interactions with St John's wort (Hypericum perforatum): an update on clinical observations. AAPS J 11(4): 710–727.

19. Borrelli F, Romano B, Fasolino I et al. 2012. Prokinetic effect of a standardized yarrow (Achillea millefolium) extract and its constituent choline: studies in the mouse and human stomach. Neurogastroenterol Motil 24(2): 164–171, e90.

20. Bulgari M, Sangiovanni E, Colombo E et al. 2012. Inhibition of neutrophil elastase and metalloprotease-9 of human adenocarcinoma gastric cells by chamomile (Matricaria recutita L.) infusion. Phytother Res 26(12): 1817–1822.

21. Campos-Esparza Mdel R, Torres-Ramos MA. 2010. Neuroprotection by natural polyphenols: molecular mechanisms. Cent Nerv Syst Agents Med Chem 10(4): 269–277.

22. Can OD, Ozkay UD. 2012. Effects of Hypericum montbretti extract on the central nervous system and involvement of GABA (A)/Benzodiazepine receptors in its pharmacological activity. Phytother Res 26(11): 1695–1700.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper **© 2012 IJFANS. All Rights Reserved, UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4 ,2022**

23. Capasso R, Mascolo N. 2003. Inhibitory effect of the plant flavonoid galangin on rat vas deferens in vitro. Life Sci 72(26): 2993–3001.

24. Capasso F, Borrelli R, Capasso R et al. 1998. Aloe and its therapeutic use. Phytother Res 12(Suppl 1): S124–S127.

25. Capasso F, Gaginella TS, Grandolini G, Izzo AA. 2003. Phytotherapy: A Quick Reference to Herbal Medicine. Springer-Verlag: Heidelberg, Germany. Capasso R, Borrelli F, Capasso F, Mascolo N, Izzo AA. 2004. Inhibitory effect of the antidepressant St. John's wort (Hypericum perforatum) on rat bladder contractility in vitro. Urology 64(1): 168–172.

26. Capasso R, Borrelli F, Montanaro V, Altieri V, Capasso F, Izzo AA. 2005. Effects of the antidepressant St. John's wort (Hypericum perforatum) on rat and human vas deferens contractility. J Urol 173(6): 2194–2197.

27. Capasso R, Fiorino F, Ascione V, Frecentese F, Borrelli F. 2006. Inhibition of rat vas deferens contractions by flavonoids in-vitro. J Pharm Pharmacol 58(3): 381–384.

28. Capasso R, Borrelli F, Aviello G, Capasso F, Izzo AA. 2008. Inhibitory effect of the herbal antidepressant St. John's wort (Hypericum perforatum) on rat gastric motility. Naunyn Schmiedebergs Arch Pharmacol 376(6): 407–414.

29. Capasso R, Aviello G, Romano B, Atorino G, Pagano E, Borrelli F. 2009. Inhibitory effect of quercetin on rat trachea contractility in vitro. J Pharm Pharmacol 61(1): 115–119.

30. Chahar MK, Sanjaya Kumar DS, Lokesh T, Manohara KP. 2012. Invivo antioxidant and immunomodulatory activity of mesuol isolated from Mesua ferrea L. seed oil. Int Immunopharmacol 13(4): 386–391.

31. Chan KF, Wong IL, Kan JW, Yan CS, Chow LM, Chan TH. 2012. Amine linked flavonoid dimers as modulators for Pglycoprotein-based multidrug resistance: structure-activity relationship and mechanism of modulation. J Med Chem 55(5): 1999–2014.

32. Cherniack EP. 2011. Polyphenols: planting the seeds of treatment for the metabolic syndrome. Nutrition 27(6): 617–623.

33. Gálvez J, Sánchez de Medina F, Jiménez J et al. 1995. Effect of quercitrin on lactose-induced chronic diarrhoea in rats. Planta Med 61(4): 302–306.

34. García-Lafuente A, Guillamón E, Villares A, Rostagno MA, Martínez JA. 2009. Flavonoids as anti-inflammatory agents: implications in cancer and cardiovascular disease. Inflamm Res 58(9): 537–552.

35. Gharzouli K, Holzer P. 2004. Inhibition of guinea pig intestinal peristalsis by the flavonoids quercetin, naringenin, apigenin and genistein. Pharmacology 70(1): 5–14.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper **© 2012 IJFANS. All Rights Reserved,** **UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4 ,2022**

Gibellini L, Pinti M, Nasi M et al. 2011. Quercetin and cancer chemoprevention. Evid Based Complement Alternat Med 2011: 591356.

36. Goh MJ, Park JS, Bae JH, Kim DH, Kim HK, Na YJ. 2012. Effects of ortho-dihydroxyisoflavone derivatives from Korean fermented soybean paste on melanogenesis in B16 melanoma cells and human skin equivalents. Phytother Res 26(8): 1107–1112.
37. Pallast S, Arai K, Pekcec A et al. 2010. Increased nuclear apoptosis-inducing factor after transient focal ischemia: a 12/15-lipoxygenase-dependent organelle damage pathway. J Cereb Blood Flow Metab 30(6): 1157–1167.
38. Park SE, Sapkota K, Kim S, Kim H, Kim SJ. 2011. Kaempferol acts through mitogen-activated protein kinases and protein kinase B/AKT to elicit protection in a model of neuroinflammation in BV2 microglial cells. Br J Pharmacol 164(3): 1008–1025.
39. Park MY, Ji GE, Sung MK. 2012. Dietary kaempferol suppresses inflammation of dextran sulfate sodium-induced colitis in mice. Dig Dis Sci 57(2): 355–363.
40. Prasad S, Phromnoi K, Yadav VR, Chaturvedi MM, Aggarwal BB. 2010. Targeting inflammatory pathways by flavonoids for prevention and treatment of cancer. Planta Med 76(11): 1044–1063.
41. Wallace TC. 2011. Anthocyanins in cardiovascular disease. Adv Nutr 2(1): 1–7. Wang W, Wang F, Yang YJ et al. 2011. The flavonoid baicalein promotes NMDA receptor-dependent long-term potentiation and enhances memory. Br J Pharmacol 162(6): 1364–1379.
42. Wasowski C, Loscalzo LM, Higgs J, Marder M. 2012. Chronic intraperitoneal and oral treatments with hesperidin induce central nervous system effects in mice. Phytother Res 26(2): 308–312.
43. Xu SL, Choi RC, Zhu KY et al. 2012. Isorhamnetin, a flavonol aglycone from Ginkgo biloba L., induces neuronal differentiation of cultured PC12 cells: potentiating the effect of nerve growth factor. Evid Based Complement Alternat Med 2012: 278273.
44. Yan RY, Cao YY, Chen CY et al. 2011. Antioxidant flavonoids from the seed of Oroxylum indicum. Fitoterapia 82(6): 841–848.
45. Zhang XH, Ma ZG, Rowlands DK et al. 2012b. Flavonoid myricetin modulates GABA(A) receptor activity through activation of Ca (2+) channels and CaMK-II pathway. Evid Based Complement Alternat Med 2012: 758097.
46. Zheng XK, Zhang L, Wang WW, Wu YY, Zhang QB, Feng WS. 2011. Anti-diabetic activity and potential mechanism of total flavonoids of Selaginella tamariscina (Beauv.) Spring in rats induced by high fat diet and low dose STZ. J Ethnopharmacol 137(1): 662–668.