

FLAVONOIDS NUTRACEUTICALS IN PREVENTION AND TREATMENT OF CANCER: A REVIEW**ROBERT LOTH, ARVIND SIVASUBRAMANIAN***

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Received: 05 September 2017, Revised and Accepted: 24 October 2017

ABSTRACT

The objective of the study was to discuss the preventive and treatment of cancer from flavonoids nutraceuticals from our daily dietary source. There has been increasing interest in the research of flavonoids from dietary sources, due to growing evidence of the versatile health benefits of flavonoids through epidemiological studies. Numerous biological activities have been reported. Some clinical trials or meta-analyses have suggested positive associations between flavonoid intake and human health. Several findings have proven that dietary flavonoids to have anticancer properties. Flavonoids due to their nontoxicity in nature and vast, broad aspect of its benefits in biological activities have been intensively studied for their health benefits also added to its abundant availability in our daily diets, for example, green leaves, fruits, red wine, and tea vegetables.

Keywords: Medicinal plants, Flavonoid, Cancer prevention, Antiproliferation, Apoptosis, Antioxidative, Multidrug resistance, Angiogenic.

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INTRODUCTION

Plants have been the backbone and foundation source of medicines since time immortal, although there has been a remarkable advancement achieved in modern pharmacology and in the field of synthetic organic chemistry, the dependency to acquire medicine through natural products still remain unchanged [1]. Given facts that in medical history the very origin of the reservoir for finding new promising and potential drugs is from plant source [2]. Recent years have shown an immense interest in herbal drugs and traditional treatments toward illness, disease, and the upsurge of its scientific studies worldwide will continue for many years to come [3]. Flavonoids are secondary metabolites polyphenolic compounds that are omnipresent in plants and as many, as more than 4000 broadly classified polyphenolic are known [4]. Since the ubiquitous presence of flavonoids in our daily diet, it is vital to evaluate its source in our food which acts as antioxidants. Due to vast health benefits are proven through the epidemiological investigation, there are increasing ongoing research about flavonoids and its impact on human health [5]. The evidence from some clinical trials suggested a positive link between human health and flavonoid intake. Now it is clear that flavonoids or many of its derivatives are acting as a chemoprevention to many common types of cancer [6]. The preventive and protective nature of flavonoids is related to their strong anticarcinogenic potential, antimutagenic, and antiproliferative [7]. They are abundantly present in all dietary vegetables and fruits (Table 1), intake of flavonoids in an average is estimated to be few 100 mg daily [8]. These compounds have displayed remarkably in almost all the area of biological activities, which might influence the dysregulated of normal processes during cancer progression. Those include antiproliferative, modulation of enzymatic activities and anti-inflammatory [9,10].

Along with numerous health benefits, flavonoids can be seen as an alternative to therapeutic agents for prevention of cancer or in chemopreventive [11,12]. In this review article mainly generalize the older and recent approaches toward treating cancer through nutraceutical flavonoids by analyzing numerous research finding on this topic.

FLAVONOIDS AND ITS ANTICANCER ACTIVITY**Epidemiological evidence on flavonoids**

The data collected from approximately 200 studies that analyze the relationship of vegetable and fruits and different type of cancers are

observed which shows exceptional improvement [13] there has been a rise of prostate cancer in the present alarming [14], participants of 477,312 adult men and women from 10 European countries. Initially, classified total dietary flavonoids intakes and individual subclasses were examine through questionnaires from center-specific validated dietary and compositing data that are collected from the Phenol-Explorer database. During an average of 11 years of follow-up, new cases of 4517 primary colorectal cancer (CRC) were identified, of which among 2869. There were 1648 rectal and colon tumors (proximal=1298 and distal=1266). No association between any CRC subtype and total flavonoid intake and also among individual flavonoid intake subclasses. Consumption of total flavonoids and its subclasses, examine from dietary questionnaires, does not prove to have shown an association with CRC development [8]. However, there have been few contrary reports of which states otherwise for nonassociation between flavonoids intake with subsequent cancer cause, in most of the epidemiological investigation [4].

Flavonoids: In vitro studies

The summarized reports on flavonoids against various diverse cell systems conducted *in vitro* and its inhibitory properties of potential anticancer activity are shown in Table 2.

Flavonoids: Clinical trials on human

The promising results of anticancer effects in preclinical studies have encouraged clinical trials of flavonoids in human. Phase I and pharmacological investigation of flavone acetic acid were conducted in early 1988, one among series of novel flavonoids tested [26].

Quercetin a flavonoid is occurring naturally with many biological activities, a dose-escalating Phase I was performed by Ferry and was found to suppress lymphocyte tyrosine kinase in 9 of 11 patients investigated. During the course of 3-week treatment with four low doses of quercetin (60 mg/m²) intravenous one patient with hepatocellular carcinoma had developed a fall in alkaline phosphatase and serum alpha-fetoprotein. A stage four ovarian cancer patient with who had not responded to six courses of cisplatin/cyclophosphamide chemotherapy shows fall in CA125 tumor marker from 295 to 55 units/ml after two treatments of intravenous quercetin (420 mg/m²) 3 weeks apart. The authors concluded to 1400 mg/m² as bolus dose, which can

Table 1: Dietary source and subclasses of flavonoids

Flavonoid subgroup	Representative flavonoids	Major food sources
Flavanonols	Taxifolin	Limon, aurantium
Flavanones	Eriodictyol, hesperitin, naringenin	Oranges, grapefruit
Flavanols	Catechin, gallicocatechin	Apples, tea
Isoflavones	Daidzein, genistein, glycitein, formononetin	Soya beans, legumes
Flavones	Apigenin, chrysin, luteolin	Parsley, thyme
Flavonols	Kaempferol, myricetin, rutin, quercetin	Onions, cherries, apples, kalebroccoli, tomato, berries, tea, red wine, tartary buckwheat

Table 2: Flavonoids and its anticancer activities on different types of cancer cell lines

Cancer	Cell	Flavonoid	References
Human oral cancer	HSC-2, HSG, SCC-25	Flavanones, isoflavans, quercetin, EGC, chalcones, EGCG, curcumin, genistein, ECG	Refs.[15]
Human breast cancer	MCF-7	Flavanones, daidzein, genistein, quercetin, luteolin	Refs.[16]
Human thyroid cancer	ARO, NPA, WRO	Genistein, apigenin, kaempferol, chrysin, luteolin, biochanin A	Refs.[17]
Human lung cancer	SK-LU1, SW900, H441, H661, haGo-K-1, A549	Flavone, quercetin	Refs.[18]
Human prostate cancer	LNCaP, PC3, DU145	Catechin, epicatechin, quercetin, kaempferol, luteolin, genistein, apigenin, myricetin, silymarin	Refs.[19,20]
Human colon cancer	Caco-2, HT-29, IEC-6, HCT-15	Flavone, quercetin, genistein, anthocyanin	Refs.[21,22]
Human leukemia	HL-60, K562, Jurkat	Apigenin, quercetin, myricetin, chalcones	Refs.[23,24]
B16 mouse melanoma	4A5	Chalcones	Ref.[25]

EGCG: Epigallocatechin gallate, ECG: Epicatechin gallate, EGC: Epigallocatechin

be administered either at weekly intervals or over 3 weeks. Phase II trials. 1700 mg/m² 3 weekly asset as the maximum tolerated dose however the vehicle, dimethyl sulfoxide was found to be unsuitable [27]. A pro-drug of quercetin (3 O(N-carboxymethyl) carbomyl-3,4 O,5,7-tetrahydroxyflavone) also known as QC12 which was synthesized went through initial Phase I trial IV, dose-escalation studies [28].

Inhibit carcinogen metabolic activation

One of the main important mechanism of how flavonoids may strive their anticancer activities are through their interaction with Phase I metabolizing enzymes, e.g., cytochrome P450, which metabolically activate and initiate vast numbers of procarcinogens reactive intermediates that can result to interact with cellular nucleophiles and finally cause carcinogenesis. Flavonoids hinder activities of isozymes (P450) such as CYP1A1 and CYP1A2 [29,30].

Antiproliferation

Antiproliferation can be achieved by inhibition of prooxidant agents that initiate tumor promotion, generally reactive oxygen species (ROS) a growth promoting oxidants acts as the main catalyst for progression and promotion of tumor to initiation stage, i.e., carcinogen metabolic to mutagens. Tumor promoters such as lipoxygenases and arachidonate metabolizing enzymes, and cyclooxygenases which are phorbol esters activate or induce prooxidant and flavonoids are specifically effective at xanthine oxidase inhibition [31].

Cell cycle arrest

Disruption in cell cycle advancement may result in the anticancer effects of flavonoids. Mitogenic signals execute cells to enter into a series of regulated steps allowing traverse of the cell cycle. During S phase synthesis of DNA occurs which separates into two daughter cells in M phase are the core features of progression in the cell cycle. The G2 phase occurs between the time of S and M phases, any errors to DNA during duplication are repaired during this phase stopping further propagation of these errors cells to daughter cells. In contrary, the G1 phase represents the duration of commitment to cell cycle progression that separates M and S phases as cells prepare for DNA duplication that further progress to mitogenic signals [4]. Cyclin-dependent kinases (CDKs) have been identified and act as the key regulators of progression in the cell cycle, deregulation and alteration of CDK activity

are hallmarks of pathogenic resulting to neoplasia. A numerous of cancers is associated with mutation of the CDK genes or CDK inhibitor genes, as a result, causes hyperactivation of CDKs. Hence, modulators or inhibitors can be of great interest to explore as novel therapeutic agents in cancer prevention and treatment [32,33].

Induction of apoptosis

Flavonoids have been known to induce cell death (apoptosis) in some cancer cell lines, while normal cells are spared. The molecular mechanisms by which flavonoids initiate apoptosis have not yet been fully understood. There can be several mechanisms factors that may be involved, which may include inhibiting the activity of DNA topoisomerase I/II activity, [23,34-36] and decrease in the ROS [37].

Initiation of differentiation

The flavones phloretin, quercetin, luteolin genistein, apigenin, and isoflavone daidzein were found to induce differentiation of human acute myelogenous leukemia HL-60 cells into monocytes and granulocytes [38,39]. Cancers cells arise by harboring mutated cells that initiate the need for exogenous growth factors. Abnormality of growth control ultimately results in the selection of clonal lines of cells that replicate at the pace of embryonic stage and yet fail to respond to maturation signals and differentiation. The nonphysiological promoter of terminal differentiation has been used as novel therapies approach toward cancer therapy and prevention. Initiation of terminal differentiation by flavonoids may result in ultimate elimination of tumorigenic cells and maintaining balance of homeostasis in a normal cell. Therefore, flavonoids could be developed into promising alternative as anticancer agents [4].

Antioxidative activity of flavonoids

Dietary flavonoids act as natural antioxidants [40] against cancer may be through the limit of damaging oxidative reactions in mutated cells, which may incline to the development of carcinoma. Oxygen-derived free radicals possess the properties to promote and initiate to carcinogenesis. Mainly lipid peroxidation products which originate from dying cells could also lead to a cancer promotional effect [41].

Prohibit angiogenic process

Flavonoids which are also known as angiogenesis inhibitors are source from nature [42].

Table 3: A recently published articles attribute some specific flavonoids or their derivatives promote cell apoptosis in cancer cells involving throughout mechanisms for the synthesis of ROS

Cell line	Molecules	Results	Mechanism of action	Refs.
B16-F10 (melanoma)	Quercetin	The pro-apoptotic effects of low doses of quercetin (10–20 μ M) in UVB-irradiated melanoma cells are mediated through the increase of ROS, calcium homeostasis imbalance, and modulation of antioxidant defense	Quercetin attenuated MEK-ERK and Akt/PI3 K signaling and enhanced the UVB-induced NF- κ B nuclear translocation	[48]
U20s (osteosarcoma)	RWP	RWP induced Type I/II mixed cell death in a dose-dependent manner with a maximum effect in the range of 100–200 μ g/ml equivalents of gallic acid	RWP mechanism was independent of its antioxidant activity and involved the inhibition of PI3K/Akt kinase signaling	[49]
SW480 (colorectal cancer)	Silibinin	Silibinin rapidly increased oxidative stress in SW480 cells due to ROS induced and generation apoptosis and autophagy mixed phenotypes	Silibinin strongly inhibited pathway of PI3/Akt/mTOR but activated MAP2K1/2-MAPK1/3 signaling for its biological effects	[50]
MDA-MB-468 (breast cancer) BxPC-3 (pancreatic cancer) PC3 (prostate cancer)	Luteolin, apigenin, EGC-3-gallate, and resveratrol	Inhibit cell proliferation and induce apoptosis	Intracellular copper mobilization and ROS generation by the tested compounds leading to cancer cell death	[51]
A549 (Lung cancer)	Curcumin mono-carbonyl analogs (diarylheptanoids)	Cytotoxic and proapoptotic mechanisms	Compound A1 convert TrxR antioxidant enzyme into an ROS promoter, resulting in a burst of the intracellular ROS. The ROS generation is associated with apoptosis	[52]
Jurkat cells (T cell leukemia)	Tetrahydroxy- <i>trans</i> -stilbene derivatives (M6, M8, M12)	Cytotoxic activity and increased activity of caspase 3 and 9	Cell death was accompanied by loss of mitochondrial potential, oxidative stress, decrease of glutathione level as well as loss of both mRNA expression and activity of superoxide dismutase (MnSOD)	[53]
B16-F10 (melanoma)	ECG analogue JP8	JP8 induces apoptosis and autophagy in B16-F10 melanoma murine cells but not in normal cells, through ROS generation	JP8 preferentially induces cell death (Type I/II) in cancer cells by increasing ROS generation and inducing stress-related proteins such as IRE1 α , p-eIF2 α and CHOP	[54]
Hepatocellular, pancreatic, breast, glioblastoma cancer cell lines	DPP 23 (novel synthetic polyphenol conjugate)	DPP 23 increases ROS generation and trigger apoptosis in cancer cell lines without effects in normal cells	DPP 23 activates the UPR in the endoplasmic reticulum through ROS generation and caspase-dependent apoptosis selectively in transformed cells	[55]

ROS: Reactive oxygen species, RWP: Red wine polyphenols, MAPK: Mitogen-activated protein kinases, UPR: Unfolded protein response, NF- κ B: Nuclear factor-kappaB, PI3K: Phosphoinositide 3-kinase, ERK: Extracellular regulated protein kinases, EGC: Epigallocatechin

In the healthy adult, human body angiogenesis is a strictly controlled process and is regulated by different endogenous angiostatic and angiogenic factors. Still, in cancer, pathological angiogenesis can occur when proper vascularization is deprived, due to the lack of diffusion of oxygen and nutrients in the cells. Apoptosis occurs to balance the high proliferation rate in the tumor. Flavonoids are able to interfere with various steps of angiogenesis as inhibitors such as lumen formation, migration of endothelial cells, proliferation, and basement destruction of blood vessels. Hence, can be potential compounds for the treatment of tumors [42,43].

Multidrug resistance (MDR) modulation

Some specific flavonoids are known to possess potent inhibitory activity against the drug-exporting activity of P-glycoprotein, adenosine triphosphate (ATP)-binding cassette (ABC) a plasma membrane transporter that evicts drugs which are cytotoxic at the expense of ATP hydrolysis. P-glycoprotein has two homologous portions each containing a transmembrane domain (TMD) involved in drug efflux

and binding, and the other half a cytosolic nucleotide-binding domain (NBD) involved in ATP hydrolysis and binding, with domain topology of an overall (TMD-NBD) 2. Modulation by flavonoids toward cell MDR mediated by P-glycoprotein may be caused by inhibiting the overexpression of MDR-1 [44].

Novel biological effects with natural killer cells

Natural killer (NK) cells were discovered as naturally occurring killer lymphocytes toward mouse Moloney leukemia cells. NK cells may function to remove virally infected and transformed cells [45]. In principle, if malignant cells escape immune surveillance, or suppress the function and numbers of NK cells, it could lead to development and establishment of cancer. In support of this idea, dysfunction and abnormal NK cells were observed in cancer patients including (i) reduced cytotoxic activity, (ii) down-regulated expression of activating receptors, cytokine, and intracellular signaling molecules, and (iii) attenuated cell proliferation [46].

Table 4: List of flavonoids with their molecular targets and chemopreventive effects

Phytochemical	Chemopreventive effect	Molecular targets	Biological effect
Tangeretin	Suppression of carcinogenesis	c-Src CYP1A2	Inhibit the activity (<i>in silico</i> study) upregulation
	Cell cycle regulation Apoptosis	p53, p21, p37 p53	on COLO 205 cells G1 arrest in MCF-7 cells Trigger apoptosis in COLO 205 cells Induce apoptosis on HL-60 cells
Nobiletin	Angiogenesis and metastasis Suppression of carcinogenesis	ERK-2 HIF1- α c-Src CYP1A2	Inhibit the activity (<i>in silico</i> study) Inhibit the activity (<i>in silico</i> study)
	Angiogenesis and metastasis Suppression of carcinogenesis	ERK-2 HIF1- α PI3K	Inhibit the activity (<i>in silico</i> study) Inhibit the activity (<i>in silico</i> study)
Hesperidin	Cell cycle regulation Apoptosis Co-chemotherapeutic	CDK2 p53 PgP, Bcl-2, Bax	Inhibit the activity (<i>in silico</i> study) Upregulation on MCF-7 cells Inhibit the activity (<i>in silico</i> study) increase cytotoxicity of doxorubicin on MCF-7 cells by modulating cell cycle and induce apoptosis Downregulation on HeLa cells. Upregulation on HeLa cells
	Cell cycle regulation Apoptosis	CDK2, CDK4, Cyclin D Caspase-3	Downregulation on MCF-7 cells Activation on HL-60 cells
	Antioxidant Suppression of carcinogenesis Cell cycle regulation	LTC4 PI3K PKC p21, ATP	Inhibit the transport Inhibit the activity (<i>in silico</i> study) Upregulation in 5637 bladder cancer cells inducing G1 arrest Bind on PI3K binding site
Hesperetin	Cell cycle regulation Apoptosis	CDK2 p53	Inhibit the activity (<i>in silico</i> study) Inhibit the activity (<i>in silico</i> study)
	Apoptosis Co-chemotherapeutic	CDK2 PgP	Inhibit the activity (<i>in silico</i> study) Inhibit the activity (<i>in silico</i> study)

ATP: Adenosine tri-phosphate, PI3K: Phosphoinositide 3-kinase, ERK: Extracellular regulated protein kinases

RECENT ADVANCEMENT OF FLAVONOIDS IN TREATMENT AGAINST CANCER

The field of dietary flavonoids as antioxidants is heading towards a new era of important transformation, papers on the effects of anticancer, including polyphenols contributed to identifying as beneficial for health. Many advancements has been achieved in recent studies of flavonoids and its effect on molecular and cellular level [47].

FLAVONOIDS IN CANCER METASTASIS AND CHEMOPREVENTION

The epithelial to mesenchymal transition (EMT) pathways (involved in cancer metastasis) have been the core focus in recent days targeting cancer prevention, resistance, and apoptosis. Conversion from adhesive state to motile state of epithelial cells marks the beginning to cancer metastasis. The anticancer efficacy of the flavonoids maybe in part due to their influence on the EMT pathway.

Flavonoids on molecular targets

Targeted treatment has always been a very promising approach towards developments of new drug research. Diseases are known to have many molecular mechanism which are regulated by abundances of certain proteins, such as hormones and receptors [57].

SYNERGISM EFFECTS OF FLAVONOIDS

Naturally occurring in dietary source flavonoid, fisetin synergizes, and paclitaxel in A549 treated to non-small lung cancer cell line shows the possible molecular mechanisms and its synergism effect between the two compounds results in the development of mitotic catastrophe maybe through the promotion and formation of multipolar spindle, the expulsion through autophagy of the cells with mitotic catastrophe, a rise in the level of autophagy, which presumably underlies the conversion from the cytoprotective autophagy (elicit by PTX or FIS alone) to the autophagic cell death. The data obtained seem to be promising to light the current understanding that the manipulation of autophagy favoring the inhibition of its cytoprotective effects and the initiation of the autophagic cell death, can be viewed as a possible anticancer therapy approach [58]. Initial approaches for colon-specific drug delivery which includes time-dependent systems, pH, microbial triggered drug delivery system and prodrugs having certain limitations, achieved few success [59]. The combination of cetuximab, an anti-EGF receptor (EGFR) monoclonal antibody and tectochrysin, a flavonoid

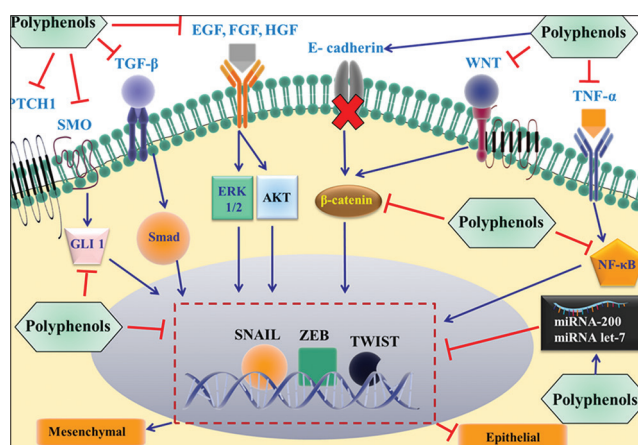


Fig. 1: Proposed mechanisms by which dietary polyphenols (phenolic acid, flavonoids, stilbenes, and lignans) inhibit EMT and cancer metastasis. The important extracellular signals are shown in the figure, and these promote by binding to individual membrane receptors from EMT, therefore activating specific EMT-inducing transcription factors (Zeb, snail, or twist). The polyphenols effect on specific proteins in signaling pathways at different levels remains to be exemplified. Transforming growth factor β , epidermal growth factor (EGF), hepatocyte growth factor, fibroblast growth factor, patched 1, smoothened, WNT, tumor necrosis factor- α , nuclear factor-kappa B cell, glioma-associated oncogene 1, and extracellular regulated protein kinases. Akt: Protein kinase B [56]

isolated from alpinia oxyphylla Miquel on human colon cancer cell growth through further hindering of EGFR pathway [60]. Furthermore, the synergy effect by combination of Wogon flavonoids with 5-FU against renal cancer or Irinotecan (CPT-11), capecitabine, or [61] naringenin and hesperetin two citrus flavonoids commonly found in grapefruit and oranges, respectively, and four non citrus flavonoids, quercetin, genistein, galangin, and baicalein were tested in one-to-one combinations and singly for their effects on growth of a human breast carcinoma cell line and cell proliferation, shows a promising results [62].

Synthesis flavonoids analogues toward anticancer activities

Flavonoids having an extensive biological effects and a broad coverage of pharmacological activities, however, the most important and prominent activity is their potential role to act as anticancer agents, in recent days, flavonoids along with their synthetic analogs have been largely examining in the treatment of prostate, pancreatic, cervical, breast, and ovarian cancer. The chemical synthetic analogs of flavonoids show to enhance or influence their anticancer activities [63] 8-isoprenyl-flavone and 7-carboxy-flavone derivatives were synthesized of their advantageous anti-inflammatory activities [64,65]. The derivatives of flavonoids when substituted by a heterocyclic or carbocyclic or radical, possessed good selectivity, cytotoxicity and an inhibitory effect against CDKs against various proliferative cell lines.[63] Proanthocyanidins which are condensed form of tannins, leucocyanidins, polymers of flavan-3-ols or oligomers consist of epicatechin units that are abundant type of proanthocyanidins in plants [66] which can be used for the prevention of tumor during the implantation of transitional cell [67], and are used to treat inflammatory conditions in skin, eyes and the mucosae [68]. Proanthocyanidins have several thousand to several ten thousands of molecular weights and can be a difficult factor in the intestine to be absorbed, however, synthesized sulfur-containing proanthocyanidin oligomer which is formed during a reaction between a plant containing compound bearing SH group and proanthocyanidins [69]. The product formed by the two compounds results in oligomer a compound with a low molecular weight that could be easily absorbed by the humans, which can be useful for lifestyle-related diseases. Variety of chalcones analogs which possess several health benefits are also synthesized [70-73].

CONCLUSIONS AND DISCUSSION

There are thousands of different types of flavonoids found in our daily dietary components. Numerous biological activities based on cancer have been reported which includes modulation of MDR, prohibition of angiogenic process, antioxidative activity, and anticancer activities. Therefore, the majority of the research has been focused on *in vitro* level, excluding pharmacology into account. The fact that the availability of flavonoids in vegetables, fruits, and plants are sustainable make its promising approach toward treatment and prevention of many major clinical diseases and offers a great opportunity in drug design and development in the near future.

Isoflavone, flavanone, flavone, and flavonol all these compounds have antiproliferative activity *in vitro* studies, and their activity varies depending on cell type employed. However, the mass productions of flavonoids are bond to its limitation considering the fact of complicated extraction methods, less extraction yield and also burdened by the cost and difficulties of epidemiological studies. Versatile approaches and strategies are being implemented to counter such limitations.

ACKNOWLEDGMENT

The authors would like to thank the Management, Sastra University, for providing the necessary facilities and the Teaching Assistantship to Robert Lotha.

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