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Revisión | Review

Antineoplastic potential of the *Vitex* species: An overview

[Potencial antineoplásico de la especie *Vitex*: una visión general]

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Abstract: Irrespective of progressive treatments, cancer remains to have the utmost rate of treatment failure due to numerous reasons associated. In recent years, the use of traditional medicine in cancer research has established considerable interest. Natural products represent an amazing source for cancer therapy and combating associated side-effects. More than thousand plants have been found to possess significant anticancer properties. *Vitex* is the largest genus in the family Lamiaceae which comprises 250 species distributed throughout world and several species have been reported to have anticancer properties. Despite a long tradition of use of some species, the genus has not been explored properly in terms of its anticancer profile. Here we are reporting the updated knowledge of the antineoplastic profile of this genus available so far. In the concluding part, the future scope of *Vitex* species has been emphasized with a view to explore its multifarious antineoplastic activities and mode of action.

Keywords: Lamiaceae; Chaste tree; Charaka samhita; Phytochemicals; Apoptosis; Toxicology

Resumen: Independientemente de los tratamientos progresivos, el cáncer sigue teniendo la mayor tasa de fracaso del tratamiento debido a numerosas razones asociadas. En los últimos años, el uso de la medicina tradicional en la investigación del cáncer ha despertado un gran interés. Los productos naturales representan una fuente increíble para la terapia contra el cáncer y la lucha contra los efectos secundarios asociados. Se han encontrado más de mil plantas que poseen propiedades anticancerígenas significativas. *Vitex* es el género más grande de la familia Lamiaceae, que comprende 250 especies distribuidas en todo el mundo y se ha informado que varias especies tienen propiedades anticancerígenas. A pesar de una larga tradición de uso de algunas especies, el género no ha sido explorado adecuadamente en términos de su perfil contra el cáncer. Aquí presentamos el conocimiento actualizado del perfil antineoplásico de este género disponible hasta el momento. En la parte final, se ha enfatizado el alcance futuro de las especies de *Vitex* con el objetivo de explorar sus múltiples actividades antineoplásicas y su modo de acción.

Palabras clave: Lamiaceae; Arbol casto; Charaka samhita; Fitoquímicos; Apoptosis; Toxicología

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INTRODUCTION

The cancer encompasess assembly of diseases involving unregulated cell growth and still remains the major cause of mortality worldwide often with poor clinical prediction. It claims more than 6 million lives each year. Methods commonly used for the treatment of cancer although possess some benefits but still there is a significant need to improve current cancer therapies and search for novel compounds (Greenwell & Rahman, 2015). To till date number of chemical as cancer chemotherapeutic agents have been created but having unwanted side effects. The foremost hurdle in cancer therapy is the damage to normal cells whereas ideally a successful anticancer drug should kill or debilitate diseased cells only. There is an unceasing necessity for new originals to use in the design of prospective chemotherapeutic agents: natural products are providing such patterns. Since ages population across the world relies on traditional remedies against a large repertoire of ailments. Conventional medications are not known to cause any remarkable derogatory effects and are readily accessible at inexpensive prices. Majority of the traditional remedies used in healthcare are achieved from plants.

The Lamiaceae, also known as mint family consist of shrubs, herbs and plants comprising about 230 genera and 7100 species mainly found in tropical and subtropical regions. This family is well known since ancient time for its ornamental, cosmetics and culinary values and most importantly medicinal uses. The genus *Vitex* is one of the prominent genera in the family Lamiaceae comprising mostly shrubs and small trees. They are common to tropical and subtropical region like Asia, Latin America and Africa (Rani & Sharma, 2013) and are reported for curing numerous ailments like, treatment of many female conditions (menstrual disorders, infertility, disrupted lactation, menopause, breast pain, acne), flatulence, vermifuge, headache, cold, migraine, eye pain, asthma, chronic bronchitis, and gastrointestinal infections such as bacterial dysentery and diarrhoea. Distinctive categories of secondary metabolites e.g., terpenes, flavonoids, iridoids, lignans, phenolic acids, anthraquinones, etc., exists in this genus (Li *et al*., 2005) which possibly attributes such activities.

This review emphasizes the antineoplastic potential of the various extracts/compounds derived from *Vitex* species as future anticancer agents. Through this review, authors intend to highlight the unexplored potential of the *Vitex* species in the cancer therapy, to till date clinical trials in the area of cancer therpy using this genus is lacking. Therefore, this genus needs to be investigated systematically so that potential species can be exploited at fullest as cancer therapeutic agents.

Limitations of the Drugs for Cancer Treatment

Advancement in the area of medical sciences has solved many hurdles in the development of cancer therapy but many are still to be solved. Treatments available depend upon the cancer type, stage and location. It involve surgery, immunotherapy, chemotherapy, radiotherapy, stem cell transformation or combination of many of them that is often complemented by unavoidable side effects. Such side effects comprise toxicity on the nearby cells and tissues, imperfect bioavailability and nonspecificity (Patra *et al.,* 2014; Mukherjee & Patra, 2016). To minimize the harmful side effects of drugs during the process of cancer therapy several measures are adapted that are focused on developing novel drug delivery approaches and targeting procedures, increasing drug accumulation and its efficacy on the lesion (Vinogradov & Wei, 2012*)*. Most of the therapeutic agents used in cancer therapy works as cytostatic and cytotoxic drugs alone or in amalgamation with additional therapies. Moreover, issues of high cost, non-ecofriendly nature and associated toxicity with such therapies is attracting the interest of cancer researchers towards phytochemicals and plant derived analogues as promising option for the better and less toxic cancer treatment (Singh *et al*., 2016).

Genus Vitex

Vitex is the largest genus in the family Lamiaceae that are basically deciduous shrubs. Interestingly, among 36 species of *Vitex*, only 16 species, i.e., *V. agnus-castus*, *V. negundo*, *V. rotundifolia*, *V. trifolia*, *V. gardneriana*, *V. ferrugenia*, *V. cannabifolia*, *V. doniana*, *V. polygama*, *V. leucoxylon*, *V. pinnata*, *V. scabra*, *V. mollis*, *V. altissima*, *V. glabrata*, *V. megapotamica* and *V. quinata* have been evaluated for their pharmacological activities (Rani & Sharma, 2013; Saklani *et al*., 2017). A list of the *Vitex* derived phytochemicals and their mechanism of action is tabulated in Table No. 1.

Table No. 1
List of the *Vitex* sp. derived phytochemicals & their mechanism of action

Name of the Species	Phytochemicals	Mechanism of action	References
Vitex agnus-castus	Flavonoids, alkaloids, saponins, catechic tannins, anthraquinones, aglycones, vitexilactone, phenylbutanone glucoside, ketosteroids, diterpenoids, iridoids, luteolin (6-C-(411-methyl-611-O-trans-caffeoylglucoside); luteolin 6-C-(611-O- trans-caffeoylglucoside; luteolin 6-C- (211–O-trans-caffeoylglucoside); luteolin- 7-O-(611-P-benzoylglucoside); 5,41- dihydroxy-3,6,7,31, tetramethoxyflavoneartemetin and isorhamnetin, vitexlactan A; 6 β-acetoxy-9 α-hydroxy-13 (14)-labden- 16,15-amide; iridoid glycosides artemetin; luteolin-7-O-β -glucuronide, 1,8-cineole, sabinene , caffeic, aetheric oils and chlorogenic acids.	Cytotoxic, apoptosis inducer, antioxidant, inhibition in cyclooxygenase-2, ameliorative effects on sexual hormones showed in amendment in testosterone and luteinizing hormone affected by prostate cancer, suppression in cancer growth rate limiting enzymes, activation of JNK and caspase-9, -3 resulted from ER stress, increase in the levels of GSH and decreased levels of serum MDA levels	Ohyama *et al*., 2003; Ibrahim et al., 2017; Odenthal, 1998; Imai *et al*., 2012
Vitex negundo	Triterpenoids, iridoids, flavonoids, tannins, steroids, cardiac and anthraquinones glycosides, protocatechuic acid; oleanolic acid; vitexin and isovitexin, ursolic acid, sitosterol, negundin-A; vitrofolal-E and vitrofolal-F, negundin-B; vitedoin-A; vitedoin-B; vitedoamine-A; δ-guaiene; guaia-3,7-dienecaryophyllene epoxide; ethyl- hexadecenoate; α-selinene; germacren-4-ol; caryophyllene epoxide; (E)-nerolidol; β-selinene; α-cedrene; germacrene D; hexadecanoic acid; p-cymene and valencene, chrysoplenetin and chrysosplenol D, negunfurol & negundonorin A.	Cytotoxic, antioxidant, suppressing growth, arresting the G_0/G_1-phase, Down-regulation of BCl_2, cyclin D1 and CDK4, reducing DNA synthesis and inducing apoptosis.	Dewade *et al*., 2010; Kannikapara-meswari & Indhumathi, 2013; Prabhu *et al*., 2013; Awale *et al*., 2011; Shubha *et al*., 2016; Zeng *et al*., 2012; Basri *et al*., 2014
Vitex rotundifolia	Flavonoids, alkaloids, saponins, iridoids, phenolics, mono- and diterpenes, α-pinene, α-terpineol, 1,8-cineole and manoyl oxide, phenylnapthalene; polymethoxyflavonoids, dehydroabietane, biformene, rotundiferan, vitexicarpin, prerotundifuranne and rotundifuranne, aucubin, thunbergol, mussaenosidic acid, trans-phytol and sabinene.	Cytotoxic, cell-cycle arrest, apoptosis inducer, antioxidant, activation c-Jun N-terminal kinase (JNK), inactivation NF-κB, caspase-3 activation	Kim *et al*., 2014
Vitex trifolia	Flavonoids, alkaloids, iridoids, anthraquinones glycosides, phenols, saponins, labdane diterpenes (vitexilactone, rotundifuran and previtexilactone), phenolic acids (*p*-hydroxybenzoic acid and vanillic acid), flavones (casticin, luteolin and artemetin), *p*-hydroxybenzoic acid, β-sitosterol, β-sitosterol-3-*O*-glucoside, casticin, and 3,6,7-trimethyl quercetagetin, vitexfolins A–C, flavonoids (luteolin, penduletin, persicogenin, artemetin, casticin and chrysosplenol-D), halimanediterpenes (vitetrifolins D–G), flavone	Cytotoxic, induced apoptosis of cells at higher concentrations and inhibited cell cycle progression at lower concentrations, antioxidant, activation, mitochondrial pathway of caspase-3 activation, activation of c-Jun N-terminal kinase, inactivation NF-κB and MAPK signalling, death receptor 5	Song *et al*., 2010; Li *et al*., 2005a; Li *et al*., 2005b; Chan *et al*., 2016; Chan *et al*., 2018

	glycosides, luteolin, ursolic acid and *m*-hydroxybenzoic acid and flavonoids such as casticin, vitexin, artemetin, coniferaldehyde and vanillin.	up-regulation, up-regulation of Bax, down-regulation of Bcl-2	
Vitex quinata	Glycosides, iridoids, flavonoids, alkaloids, saponins, phenolics, terpenes, (*S*)-5-hydroxy-7,4′-dimethoxyflavanone, (*S*)-isosakuranetin, 2′-hydroxy-4,4′,6′-trimethoxychalcone, 2′,6′-dihydroxy-4,4′-dimethoxychalcone, 3,5-dihydroxy-7,4′-dimethoxyflavonone, rhamnocitrin, (-)-loliolide, methyl 3,4-*O*-dicaffeoylquinate, methyl 3,5-*O*-dicaffeoylquinate, methyl 4,5-*O*-dicaffeoyl quinate, methyl 3,4,5-*O*-tricaffeoyl quinate, and β-sitosterol.	Cytotoxic, suppressing growth	Chen & Gilbert, 1994; Cheng *et al*., 2007; Deng *et al*., 2011
Vitex leucoxylon	Steroids, terpenoids, flavonoids, nonyl aldehyde, 3-nonanone, coumarin, maltotriose hydrate, maltopentaose hydrate, tridecanal, sorbitanmonolaurate, gamma-cyclodextrin hydrate, lanatoside A, dodecyl aldehyde, tricontane, propionic acid, phenyl sulfone, butyramide, benzenesulfinic acid, alkaloids, cardiac glycosides, gums and mucilage.	Cytotoxic, suppressing growth, break down of chromatin and induction of cell death.	Nagarathna *et al*., 2016; Meena *et al*., 2011

Anticancer profile of the Vitex species

Vitex agnus-castus

Vitex agnus-castus is also called *Vitex*, Chaste Tree, Chaste berry and Abraham's Balm (Ono *et al*., 2008). Its ripened fruits have been used as a folk medicine since long time for alleviation and/or improvement of symptoms from obstetric and gynecological diseases (Jarry *et al*., 2006).

The cytotoxic effect of ripened Israeli-grown Vitex agnus-castus fruits extract (Vitex extract) was reported on the V-79 cells (Chinese hamster lung carcinoma cells) line (Hirobe et al., 1997). It was subsequently reported that an ethanol extract of dried ripe Vitex agnus-castus fruits exhibits cytotoxic action in dose dependent manner (10-70 μg/ml) against six human cancer cell lines namely: ovarian cancer (SKOV-3), human uterine cervical canal fibroblast (HCF), uterine cervical carcinoma (SKG-3a), gastric signet ring carcinoma (KATO-III), breast carcinoma (MCF-7), lung small cell carcinoma (Lu-134-A-H) cells and colon carcinoma (COLO 201) as evident by DNA laddering and caspase activation (Ohyama *et al*., 2003). After a decade it was analyzed that crude extracts of Vitex agnus-castus seeds (300 g ml-1) too have potent antioxidant, cytotoxic and apoptotic activity evident by apoptotic cell morphology and DNA damage in a concentration dependent manner (Aslantürk & Çelik, 2013).

Additionally, a recent finding where Vitex berries crude extract was prepared and tested against human prostate cancer cell line (PC3) and then incorporated into in vivo model for prostate cancer induced chemically in rats. Their results suggested that this extract could cure prostate cancer (IC50=6.90 μg/ml, IC90=14.40 μg/ml) with induction of apoptosis without any signs of toxicity, also it can reduce the relative risk to prostate cancer when it used in benign prostate hyperplasia, as a preventive agent (Ibrahim *et al*., 2017).

The antineoplastic properties of *Vitex* extract against prostate cancer may be due to its influence against cancer risk factors; antioxidant and anti-inflammatory characters, ameliorative effect on sex hormones and suppression in cancer growth rate limiting enzymes (Ibrahim *et al*., 2017). Recently it was reported that there is regression in the tumor of the rats treated with *Vitex agnus-castus* extract (200 mg per kg body weight for 15 days) denoting the positive treatment of mammary tumor and improved oxidative status of the tissue as evident by increase in the levels of GSH and decreased levels of serum MDA levels as an indicator of reduced oxidative stress (Kour, 2017). However, still there is big debate about the role of antioxidants especially in cancer. Many study contradicts the old saying that antioxidants prevents cancer. A study by Sayin *et al.*,

2014 reported that antioxidants accelertae lung cancer progression by inactivation of ROS and p53, a tumor supressor. Another group of researchers (Le Gal *et al.,* 2015) demonstrate that antioxidants can increase melanoma metastasis in mice by increasing the ratio between reduced and oxidized glutathione. This might be due to the fact that primary mechanism of many chemotherapeutic drugs against cancer cells is the formation of ROS or free radicals (Tarlovsky *et al.,* 2013) and administration of antioxidants quenches ROS and inactiavtes p53 thus promoting cancer cell growth. Therefore, a study in the area of *Vitex* induced cytotoxicity and its antioxidant profile is required that could explore its dual action for its further use.

Vitex negundo

Use of *Vitex negundo* has been reported in Charaka Samhita, the most primal text book of Ayurveda, Chinese and in Unani conventional medication schemes. *Vitex negundo* is also known as the five-leafed chaste tree or monk's pepper (Rani & Sharma, 2013). In a study the effect of ethanol and aqueous extract (200 mg/kg) of leaves of *Vitex negundo* against Dalton's ascitic lymphoma (DAL) in swiss-albino mice and Ehrlich's Ascite Carcinoma (EAC) tumor bearing mice was analyzed using 5 - fluorouracil (20 mg/kg) as standard drug. It was found that extract treatment reduces the tumor weight and hence increased the life duration of diseased mice and haematological parameters also revived towards normal level. (Dewade *et al*., 2010; Kannikaparameswari & Indhumathi, 2013). Interestingly in other study green silver nanoparticles were synthesized from leaf extract of *Vitex negundo* L. and evaluated for growth-inhibitory effect on human colon cancer cell line HCT15. It was found that these nanoparticles arrested HCT15 cells at G_0/G_1 and G_2/M phases with corresponding decrease in S-phase thus hinting that it may exert its antiproliferative effects by suppressing growth, arresting the G_0/G_1-phase, reducing DNA synthesis and inducing apoptosis with an IC_{50} of 20 µg/ml at 48h incubation (Prabhu *et al*., 2013). Furthermore, isolation of the active constituent's chrysoplenetin and chrysosplenol D from *Vitex negudo* and their cytotoxic activity against PANC-1 human pancreatic cancer cells and against a panel of 39 human cancer cell lines was performed. The COMPARE analysis suggested that the molecular mode of action of chrysoplenetin was unique compared with the existing anticancer drugs (Awale *et al*., 2011). The antileukemic activity of the chloroform extract from *Vitex negudo* was tested on HEL92.1.7 and Jurkat cell lines (IC_{50}=291.5 µg/ml) and the results showed good antioxidant and antiproliferative activity (Shubha *et al*., 2016).

Another study reported antiproliferative effect of methanolic leaf extracts of *Vitex negundo* on MDA-MB-231(non-hormone dependent human breast cancer cell line) with IC_{50} values 65.38 µg/mL (Salleh *et al.,* 2014). Out of six terpenes isolated from *Vitex negundo* were evaluated for their cytotoxicities against four cancer cell lines that revealed that negunfurol was the most active compound against HL-60 with IC_{50} value of 0.94 ± 0.26 µg/mL and negundonorin A was highly cytotoxic to ZR-75-30 cells with IC_{50} value of 0.56 ± 0.19 µg/mL (Figure No. 1) (Zheng *et al*., 2012a).

Vitex rotundifolia

Vitex rotundifolia is a sprawling shrub with round leaves and spicy fragrance. It has long been used as an anti-inflammatory herb in traditional Chinese medicine. It has also been reported that vitexicarpin can inhibit the growth of various cancer cells. Casticin or vitexicarpin (Figure No. 1), a flavonoid isolated from fruits of *Vitex rotundifolia* exhibited considerable growth inhibition, cell-cycle arrest and apoptosis against human lung cancer cells (PC-12) and human colon cancer cells (Ono *et al*., 2002), human cervical cancer cell line Hela (Chen *et al*., 2011; Zheng *et al*., 2012), hepatocellular carcinoma cell line HepG2 (Yang *et al*., 2011; He *et al*., 2013), lung epithelial cell line 549 (Koh *et al*., 2011) and leukemic cell line K562 (Shen *et al*., 2009). It induces apoptosis via plethora of factors like, activation c-Jun N-terminal kinase (JNK), inactivation NF-κB, Caspase-3 activation in cell specific manner. It has been reported that G2-M arrest by casticin (IC_{50}=0.23 µM) may be linked to its antimitotic activity as evident by disrupted mitotic spindles in immunostaining (Kobayakawa *et al*., 2004). Another compound Rotundifuran (Figure No. 1), a labdane type diterpene from *Vitex rotundifolia* was reported to induce apoptosis in human myeloid leukaemia cells (HL-60) with IC_{50}=22.5 µM (Ko *et al*., 2001). In a recent study it has been reported that *Vitex rotundifolia* fruit suppresses the proliferation of human colorectal cancer cells through down-regulation of cyclin D1 and CDK4 via proteasomal-dependent degradation and transcriptional inhibition (Song *et al*., 2018). Moreover, it induces apoptosis through the down regulation of ATF3-Mediated Bcl-2 expression in these cells (Song *et al*., 2017).

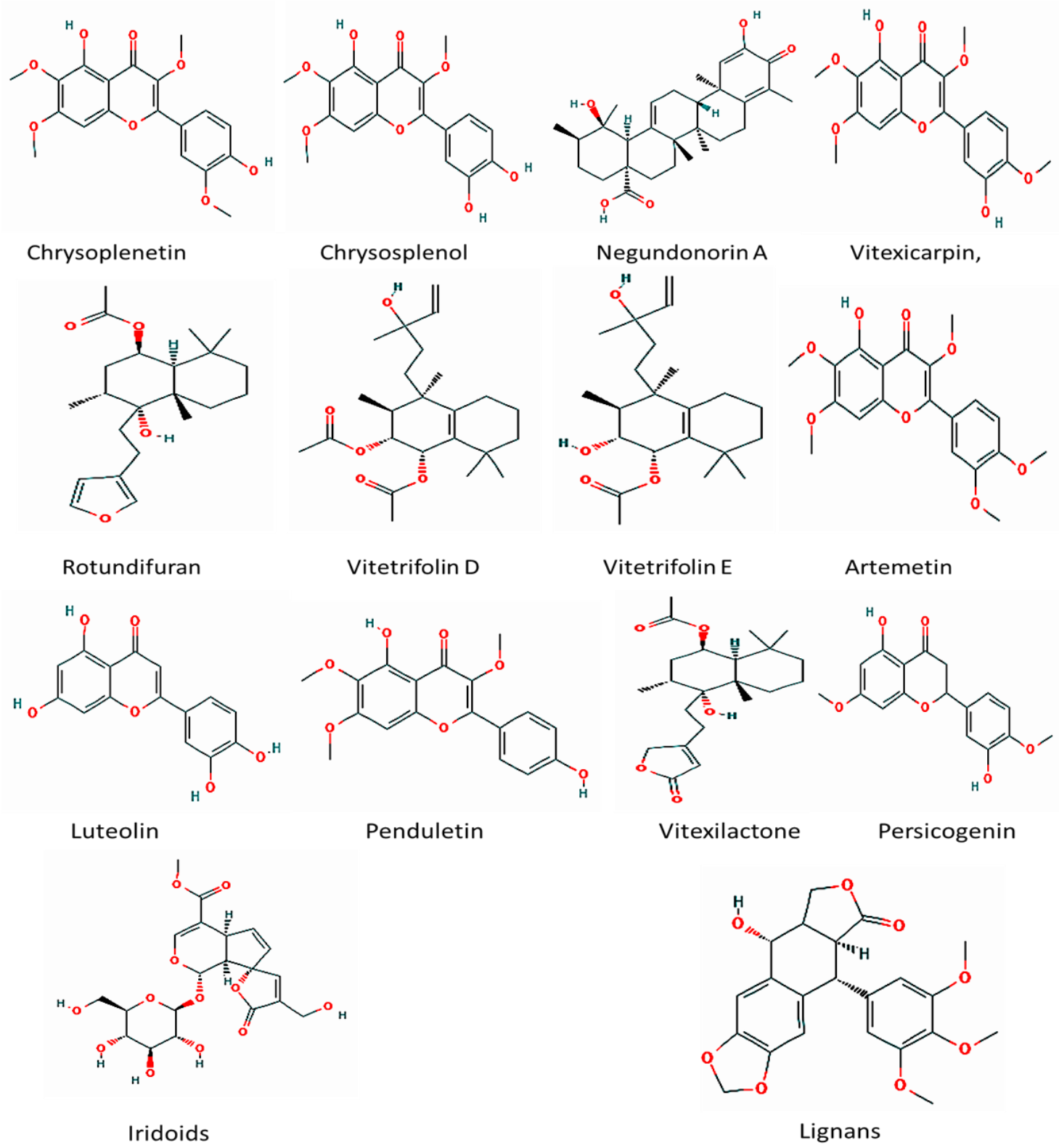

Figure No. 1
Chemical structure of some important antitumor compounds from *Vitex* spp
Source: https://www.ncbi.nlm.nih.gov

Vitex trifolia

Vitex trifolia is a fast-growing shrub with variegated foliage with white marginal variegation and pretty blue flowers. These soft leaves smell pungent when crushed. It is used as Chinese folk medicine since time immemorial. It has been reported that several flavonoids (persicogenin, artemetin, luteolin, penduletin, vitexicarpin and chrysosplenol-D) (Figure No. 1) isolated from *Vitex trifolia* inhibit cell cycle progression at G2/M phase and induce apoptosis in mammalian cancer cells (Li *et al*., 2005a). vitexicarpin (at concentration >0.2 µl/L) surprisingly has been reported to affect proliferation and apoptosis in mutated p53 breast cancer cell (Song *et al*., 2010). Moreover, five labdane-type diterpenes, vitexilactone, (rel5S,6R,8R,9R,10S)-6-acetoxy-9-hydroxy-13(14)-labden-16,15-olide, rotundifuran, vitetrifolin D, and vitetrifolin E (Figure No. 1) isolated from *Vitex trifolia* has been reported to induce apoptosis both on tsFT210 and K562 cells at higher concentrations while at lower concentrations they inhibited the cell cycle progression at the G_0/G_1 phase (Li *et al*., 2005b). It has been reported that the hexane and the dichloromethane extracts of aerial parts of *Vitex trifolia* were cytotoxic to SQC-1, OVCAR-5, HCT-15 and KB cancer cells (Chan *et al*., 2016). Moreover, fruits have also been reported to have an anticancer profile (Chan *et al*., 2018).

Vitex quinata

Vitex quinata is a 4-12 m tall evergreen tree found mainly in temperate and tropical Asia (Chen & Gilbert, 1994). Another study on *Vitex quinata* led to the isolation of five compounds, namely, daucosterol, 3,5-*O*-dicaffeoyl quinic acid, 20-hydroxyecdysone 20, 22-monoacetonide, β-sitosterol and vitexin, but with no biological data reported (Cheng *et al*., 2007). Application of the leaf extract of *Vitex quinata* on the MCF-7 human breast cancer cell line, led to the isolation of a new δ-truxinate derivative and a new phytonoic acid derivative, together with 12 known compounds. The structures of the new compounds were determined by spectroscopic methods. In a cytotoxicity assay, S-5-hydroxy-7,4'- dimethoxy-flavanone was found to be the sole active cytotoxic compound, when tested against LNCaP hormone-dependent prostate, Lu1 human lung, and MCF-7 human breast cancer cells with ED_{50} values of 6.7, 4.7, and 1.1 µM, respectively.

Vitex leucoxylon

This plant is a large deciduous tree, with a thick trunk and a spreading crown found almost throughout the Indian Deccan peninsular region. In a study it was reported that the administration of steroids of *Vitex leucoxylon* (at 100 and 200 mg/kg for 12 days) together with 5-fluorouracil (20 mg/kg for 12 days) considerably decreased the total number of cells, tumor volume and viable cell count. The steroids of *Vitex leucoxylon* induced chromatin condensation, nuclear damage and cell death which may be connected to slower tumor growth. Moreover, it also improves the antioxidant status of the treated subjects (Nagarathna *et al*., 2016).

It is evident from the above-mentioned studies and literature survey that *Vitex* derived phytochemical acts on plethora of cancer molecular targets, only in vitro, and without clinical assays, (Figure No. 2) depending on the cell types, thus leading to eventual inhibition of growth or destruction of cancer cell. However, detail of the intricate molecular network involved and their interlinking with other signal transduction pathways still has to be explored at molecular level so that it would be useful for the fullest exploration of such compounds.

Toxicology

Adverse effects of most of the *Vitex* species have been reported to be mild and reversible. The frequently observed ones include: menstrual disorders, dry mouth, acne, mild gastrointestinal complaints, fatigue, nausea, itching of skin, and erythematous rash (Rani & Sharma, 2013). Leaf extracts of *Vitex negundo* showed no histomorphological alterations in the stomach of rats but causes gastric damage through prostaglandin inhibition (Tandon & Gupta, 2004).

There has an ambiguity about the effect of *Vitex agnus-castus* on lactation as to whether it increases or decreases lactation (Daniele *et al*., 2005). Interestingly, *Vitex rotundifolia* (beach *Vitex*) fruits have been shown to transfer cuticular alkanes to the sand resulting in intense sand hydrophobicity, thus ecosystem damage through the exclusion of native plant species and it is also associated with potential negative effects on sea turtle nesting too (Cousins *et al*., 2009). In another interesting report the acute study was performed in mice using the combined extracts of *Vitex leucoxylon, Vitex negundo and Vitex trifolia* (at doses of 200 and 400 mg/kg for 28 days od daily administration) where it no toxicity was found on considering the effect on haematological, liver parameters, other biochemical parameters such as total protein, albumin and globulin and electrolytes level (Phani & Kumar, 2014).

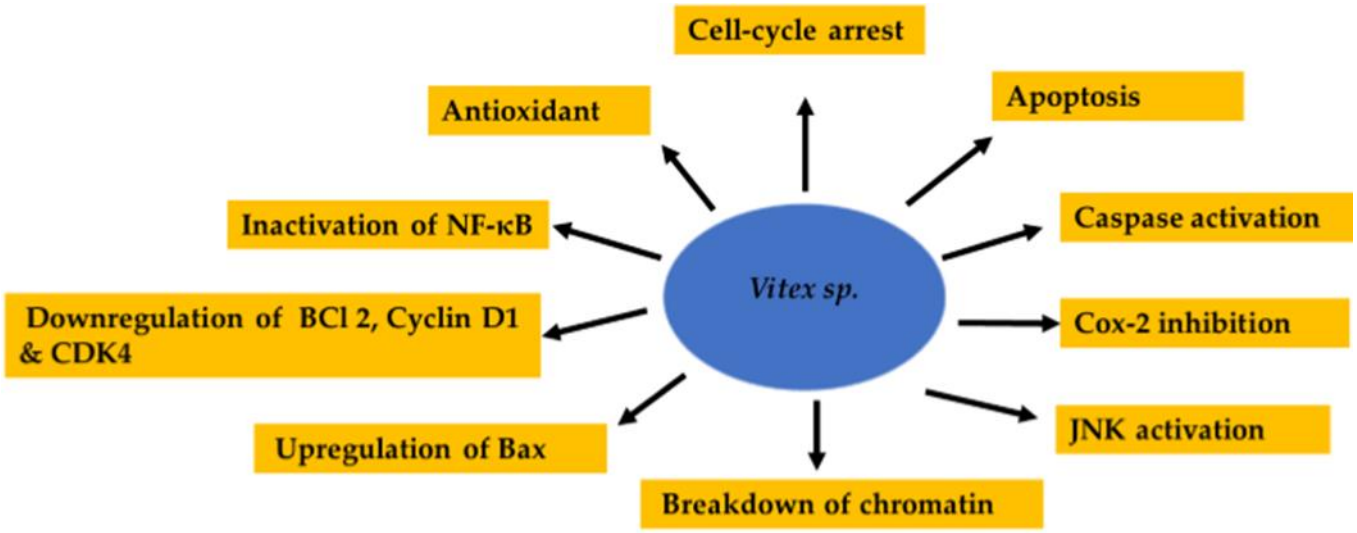

Figure No. 2
Schematic representation of the molecular targets of *Vitex* spp. derived phytochemicals on cancer cell

CONCLUSION

Besides, maintaining the health and vitality, plants derived components have played an important role in the development of several clinically useful anticancer agents. Keeping in mind the current hurdles in cancer chemotherapy (Schaffhausen, 2015) i.e. unavoidable side effects on normal cells, resistance, cardiotoxicity and high cost, there is a need for new plant-derived bioactive agents; thus, genus *Vitex* may be an important natural source for the development of new drugs and may provide a cost-effective means of treating the cancer in the developing world.

In this updated review, we have summarized the biological findings on the anticancer potential of the known phytochemical constituents of the *Vitex* spp. so far. These conclusions indicate that this genus is a treasured source of bioactive molecules. Phytochemical and pharmacological studies of the active anticancer compounds isolated from the genus *Vitex* have fascinated more attentiveness in recent years. Considering the many bioactive compounds isolated from the plants in this genus, further explorations on their pharmacological effects are very obligatory. Thus, the promising pharmacological activities should be confirmed by studies at pre-clinical and clinical levels. In addition, authenticating the interactions amongst chemical components, pharmacological outcomes and traditional usages of plants in this genus is still remains a fundamental undertaking and should be paid more consideration to.

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