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REVIEW ON SCOPOLETIN: A PHENOLIC COUMARIN WITH ITS MEDICINAL PROPERTIES

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ABSTRACT: Scopoletin (7-hydroxy-6-methoxy coumarin) is a phenolic coumarin isolated from many plants, known as an important compound of the phytoalexin group. This article is created to provide information regarding the synthesis and pharmacological activity of scopoletin. Scopoletin has been found in many plant species and isolated from various parts of the plant (roots, fruits, leaves, stems, etc.) such as *Morinda citrifolia*, *Aegle marmelos*, *Erycibe obtusifolia* Benth, *Lasianthus lucidus* Blume, *Melia azedarach* L., *Sinomonium acutum*, *Convolvulus prostratus*, and *Solanum lyratum*, *etc.* which all possess a number of medicinal properties. Its various pharmacological activities have been reported through a number of investigations. It is reported that such compounds produced specific biological activities and possible health implications for humans in food and medicine. Pharmacological activities that are established *in-vivo* are antithyroid, antihypertensive, anti-proliferative, anti-inflammatory, neuro-logical, anti-dopaminergic and anti-adrenergic, antidiabetic drug, and anti-hyperuricemic activities. Based on *in-vitro* studies, scopoletin has pharmacological activities, including an antihepatotoxicity, antibacterial, antifungal, antitubercular, and antioxidant. From the assorted pharmaco-logical activities of scopoletin, it has the potential to be further developed.

INTRODUCTION: Scopoletin (7-hydroxy-6-methoxy coumarin) is a phenolic coumarin isolated from many plants, known as an important compound of the phytoalexin group. It has a yellow crystalline structure with a molecular weight of 192 and a melting point of 204–206 °C. Its various biological activities have been reported through a number of investigations. Booth *et al.,* (2004) reported that such compounds produced specific biological activities and possible health implications for humans in food and medicine.

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In clinical uses, scopoletin and the substance class of coumarins were described and tested for treating anticonvulsant properties, cardiovascular and neuromuscular symptoms as well as an anti-diabetic agent use in alleviating insulin resistance and anticoagulant.

For infectious diseases, coumarins and scopoletin were described as potentially exhibiting anti-bacterial activity against bacteria such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus cereus*, and *Escherichia coli*. In an animal model study, Panda and Kar (2006) demonstrated that scopoletin at a low dose had the potential to regulate hyperthyroidism and hyperglycemia. Obasi *et al.* (1996) and Moon *et al.* (2007) suggested the possible role of dietary scopoletin in some disorders of blood clotting and lipid metabolism in animals and effects on inflammation

acting on mast cells. Scopoletin has served an important role for a long time in traditional medicine in Africa, Asia, and Europe. Several plant families, *e.g.,* Aceraceae, Asteraceae, Euphorbiaceae, Fabaceae, Rubiaceae, Combretaceae, Meliaceae, Rutaceae, Solanaceae, *etc.* contain high yields of scopoletin and are used as medicine for convulsion symptoms and rheumatic pain.

The fruit and seeds of Tetrapleura tetraptera (Fabaceae) are used in Nigeria and Ghana, while the fruit of *Physalis alkekengi* (Solanaceae) is used to reduce inflammation in Colombia. The juice from the fruits and leaves of *Morinda citrifolia* (Rubiaceae), namely known as "Noni" in the Asia Pacific, are used for the treatment of diabetes, regulation of blood pressure and as a poultice on wounds. In 2003, the official journal of the European Union reported that the European Commission approved that "Noni" fruit juice was a novel and safe health food in Europe.

In addition, Nawrot *et al.* (2013) and Dai *et al.* (2018) reported that scopoletin isolated from the stem bark of Cedrelopsis rakotozafyi Cheek & Lescot (Rutaceae) used as febrifuges or reduce fevers. Additionally, the new coumarins were discovered from the roots of *Terminalia trophophylla* H. Perrier (Combretaceae), and the stem bark of Astrotrichilia sp. (Meliaceae) revealed potentially activities against A2780 human ovarian cancer cell line [1].

Scopoletin plays a major role in treating various diseases. Scopoletin possess anti-aging [2], acaricidal [3, 4], anti-amyloidogenic [5], anti-angiogenic [6], anti-anxiety [7], anti-arthritic [8, 9], anti-bacterial [1], anti-cancer [10, 11, 12, 13], anticonvulsant [14], anti-cholinesterase [15], anti-depressant [16], anti-diabetic [17, 18], antidopaminergic-antiadrenergic [19], anti-fungal [20, 21], anti-hepatosteatosis-anti-obesity [22, 23], anti-hypertensive [24], antihyperuricemic [25], anti-inflammatory [15, 22, 26, 27, 28], anti-microbial1, anti-migratory [12], antioxidant [15, 29, 30, 31], anti-proliferative [32], anti-termite [33], anti-thyroid [30], anti-tubercular [34], anti-tumor [6, 35, 36, 37, 38], hepato-protective [39], neuroprotective [5, 40, 41, 42] activities and it also plays an important role in esophagitis, gastric ulcer [43] and neurologicaldisorders [44]. All these pharmacological activities of scopoletin are already reported.

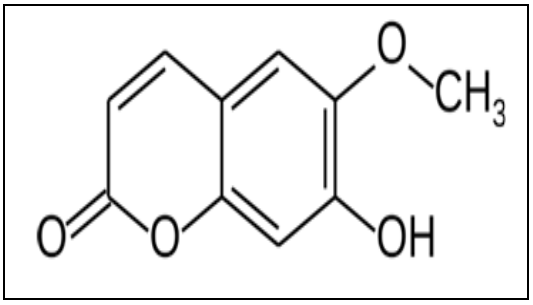

FIG. 1: CHEMICAL STRUCTURE OF SCOPOLETIN

Source of Scopoletin: Scopoletin (7-hydroxy-6-methoxy coumarin) is a phenolic coumarin isolated from various parts of the plant (roots, fruits, leaves, stems, *etc.*) such as *Acer saccharum* Marsh [45], *Aegle marmelos* [30], *Aleurites moluccana* (L.) [46], *Arabidopsis thaliana* [47], *Artemisia annua* [48], *Artemisia feddei* [49], *Artemisia iwayomogi* [50], *Brunfelsia hopeana* [51], Canscora decussate [52], *Chenopodium murale* [53], Cirsium setidens [54], *Clausena excavate* Burm.f. (Pyin-daw-thein) [55], *Convolvulus prostrates* [56], *Erycibe obtusifolia* Benth [9], *Fagraea ceilanica* [57], *Gossypium hirsutum* [58], *Hevea brasiliensis* [59], Hedyotis cap*itellata* [60], *Helianthus anuus* [61], *Helichrysum italicum* [62], *Hymenodictyon floribundum* [63], *Hymenodictyon obovatum* [64], *Hypochaeris radicata* [65], *Ipomoea batatas* [66], *Ipomoea digitata* [67], *Ipomoea r*eniformis [68], *Lasianthus lucidus* Blume1, *Macaranga gigantifolia* Merr [69], *Magnolia fargesii* [70], Manihot esculenta [71], *Melia azedarach* L. [20], *Morinda citrifolia* [12], *Morus alba* L. (Po-sa) [72], *Nicotiana tabacum* [73], *Scaphopetalum thonneri* [74], *Sinomonium acutum* [29], *Solanum lyratum* [39], *Tetrapleura te*traptera [75], *Tilia cordata* Mill [76], *Ulmus pumila, Ulmus campestris* [77], *Viburnum tinus* [78].

Synthesis of Scopoletin: Here, we describe a new method to prepare scopoletin by the Knoevenagel–Doebner reaction, which can effectively produce copoletin on a large scale. The preparation method is very simple, and all reagents are commercially available. The intermediate 2,4-dihydroxy-5-methoxy-benzaldehyde(5)was obtained in a one-step reaction from2,4,5-trimethoxybenzaldehyde (4) by reaction with aluminium (III)chloride in dichloromethane, followed by acid hydrolysis. Treatment of 5 with malonic acid in pyridine for 24 h at room temperature (rt) using phenylamine as catalysts afforded 7-hydroxy- 6-methoxy-2-oxo-2H-chromene-3-carboxylic acid (6) in 86% yield.

Then heating (6) in a pyridine/ethylene glycol mixture (1:1.1) to reflux for 3 h gave scopoletin (7). Reagents and conditions: (a) $AlCl_3$ CH_2Cl_2, rt, 24 h; (b) malonic acid, phenylamine, pyridine, rt, 24 h; (c) pyridine: ethylene glycol (1:1.1); (d) 3a–j, K_2CO_3, acetone, reflux, 2 h [37].

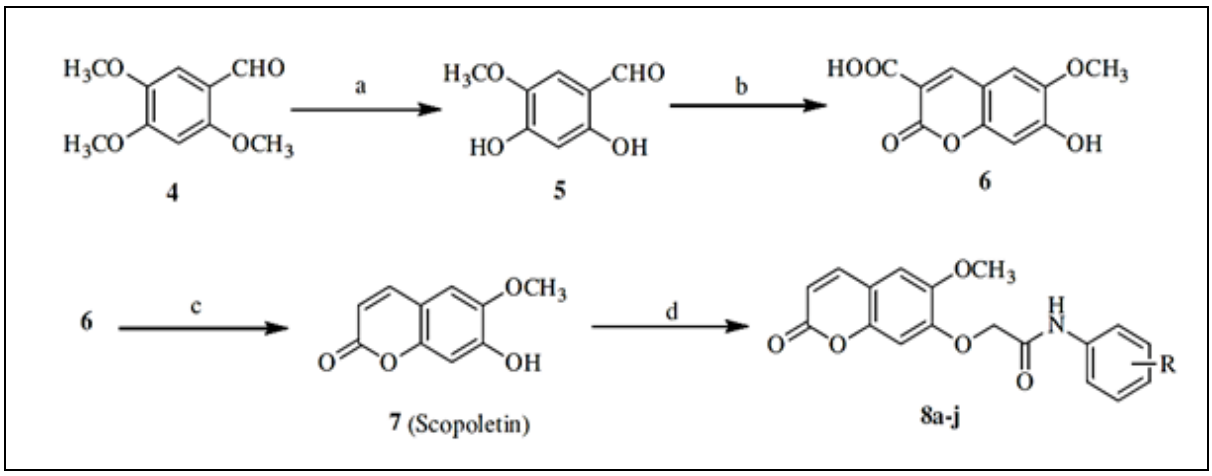

FIG. 2: SYNTHESIS OF SCOPOLETIN

Pharmacological Activity of Scopoletin:

Anti-Aging Activity of Scopoletin: Scopoletin promotes the induction of autophagy through the inactivation of p53 by the enhanced expression of histone deacetylases related to s aging. In addition to inhibition of NF-kB, Scopoletin also promotes the transportation of FoxO transcription factor into the nucleus through Akt, leading to induction of autophagy and longevity in human lung fibroblasts. Therefore, our results provide evidence that Scopoletin could influence the expression of reprogramming genes, indicating that Scopoletin could become a potential candidate for anti-aging [2].

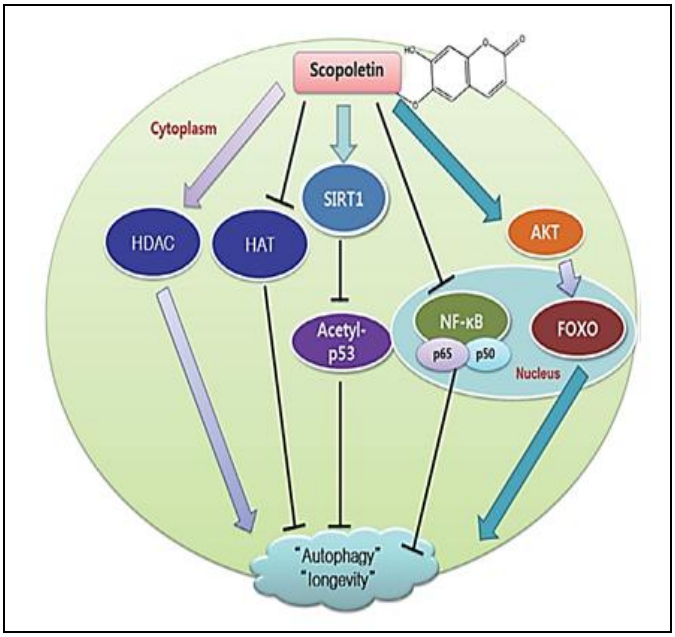

FIG. 3: EFFECT OF SCOPOLETIN ON AUTOPHAGY SIGNALING PATHWAY

Acaricidal Activity of Scopoletin: Scopoletin is a promising acaricidal compound whose acaricidal mechanism may occur by disrupting intracellular Ca^{2+} homeostasis and calcium signalling pathways [3]. Thirty phenolic ether derivatives of scopoletin, including twelve compounds with amide groups, were synthesized successfully using a molecular hybridization method. Their acaricidal activities, QSAR, molecular docking, and silico ADME properties were investigated. Some of these compounds exhibit more pronounced acaricidal activity than scopoletin, especially compounds 32, 20, 28, 27, and 8 exhibited about 8.41-, 7.32-, 7.23, 6.76-, and 6.65-fold higher acaricidal potency than scopoletin.

Compound 32 possessed the most promising acaricidal activity and exhibited about 1.45-fold higher acaricidal potency against *T. cinnabarinus* than propargite. The statistically significant 2D-QSAR model supports the observed acaricidal activities and reveals that polarizability (HATS5p) was the most important parameter controlling bioactivity. 3D-QSAR results show that bulky substituents at R4, R1, R2 and R5 (C6, C3, C4, and C7) positions, positive electron groups at the R5 (C7) position, hydrophobic groups at the R1 (C3) and R2 (C4), H-bond donors' groups at R1 (C3) and R4 (C6) will increase their acaricidal activity, which provide a good insight into the molecular features relevant to the acaricidal activity for further designing novel acaricidal agents. Molecular docking demonstrates that these selected

derivatives display different bide modes with TcPMCA1 from lead compounds, and they interact with more key amino acid residues than scopoletin. *In-silico* ADME properties study of scopoletin and its phenolic ether derivatives were also analyzed and showed potential to develop these compounds as good acaricidal candidates [4].

Anti-amyloidogenic Activity of Scopoletin: Amyloid β 42 anti-aggregation at monomer, oligomer, or protofibrils stage is an important pathological target to combat AD pathophysiology. Thioflavin (ThT) fluorescence assay was used to analyze the anti-amyloidogenic potential of scopoletin along with the evaluation of redshift in CR dye-binding assay. Amyloid β 42 protofibril-bound ThT probe fluoresces brightly at 480 nm (emission), whereas free ThT molecules would quench at the same excitation wavelength (450 nm); therefore, the fluorescence intensity would give a quantification of amyloid fibril formation. Scopoletin significantly inhibited the formation of Aβ42 fibrils in a concentration-dependent manner (11-44 μM), with 56% inhibition in fluorescence by scopoletin as compared with the control sample (Aβ42 only). The positive control, tannic acid, was observed to inhibit Aβ42 aggregation up to 85%. The emission spectrum (400-650 nm) for ThT fluorescence further reinforces antiaggregatory activity of scopoletin. Amyloid β 42 fibrils bound to ThT probe showed fluorescence emission maxima at 480 nm, whereas the Aβ42 samples treated with scopoletin concentrations (11-44 μM) showed reduced concentration-dependent fluorescence intensity at 480 nm directly proportional to the less amount of Aβ42 fibril formation. Furthermore, redshift (from 480 to 500-550 nm) in CR dye absorption assay signifies Aβ42 fibril formation.

The results of spectral shift assay also support the ThT determination of Aβ42 fibril inhibition. The typical absorbance of CR assay peaked at 490 nm, whereas when Aβ42 added to CR, the absorbance wavelength is shifted to 520 nm. Amyloid β 42 fibrils incubated with scopoletin, demonstrated reduced CR red shift close to 510 nm proving anti-amyloidogenic potential of scopoletin [5].

Anti-angiogenic Activity of Scopoletin: Scopoletin possesses strong anti-angiogenesis activity in animal models. Further, the inhibitory effect of scopoletin was exploited to demonstrate its remarkable antitumorigenic activity in a human tumor xenograft model. Histological and immune histochemical analysis of excised tumors revealed that scopoletin displayed drastic suppression of tumor vasculature. In addition, the computational simulation models showed that scopoletin has strong binding efficiency with the angiogenic factors ERK1, VEGF-A, and FGF-2 and that it is configurationally compatible with the active sites of the tested angiogenic ligands. Thus, it can be concluded that the anti-angiogenic effect of scopoletin functions by regulating ERK1, VEGF-A, and FGF-2 signalling pathways [6].

Anti-anxiety Activity of Scopoletin: Scopoletin ameliorates anxiety-like behaviors induced by CFA injection in mice. Our findings suggest that the prevention of the NF-κB and MAPK signalling pathways involving anti-inflammatory activities and regulation of the excitatory/ inhibitory balance attributes to the anti-anxiety effects of scopoletin. In short, Scopoletin should be considered as a potential agent for further development in the treatment of anxiety, and other mechanisms involved in the processes described here should be investigated to offer some new targets for anti-anxiety drug research [7].

Anti-arthritic Activity of Scopoletin: Scopoletin is the main constituent of coumarin found in the stems of *Erycibe obtusifolia* Benth, a traditional Chinese medicine used in the treatment of rheumatoid arthritis. Scopoletin has anti-arthritic effects *in-vivo,* and the effects may be mediated by anti-angiogenic alterations in the over-expression of angiogenic inducers such as IL-6, VEGF, and FGF-2. Scopoletin could significantly decrease the production of IL-6 in FLS from AA rats, which provided a reasonable explanation for its inhibitory effects on chronic inflammation in RA. The underlying mechanisms responsible for the action of scopoletin probably involve the prevention of MAPK, PKC, and CREB phosphorylation [8]. Scopoletin may be one of the active principles of E. obtusifolia Benth in rheumatoid arthritis therapy, and this study shows that treatment with scopoletin is a useful approach to the reduction of neovascularization in arthritis [9].

Anti-bacterial Activity of Scopoletin: The scopoletin isolated from stem bark lipophilic extracts of *L. lucidus* showed significant antibacterial properties in a similar manner; from this action morphological changes could be observed on bacterial cells after treating with compounds. The lipophilic extracts showed pronounced from several plants in the genus Lasianthus (Rubiaceae) have inhibited pathogenic bacteria, especially in strains of *P. aeruginosa* and which one related to traditional infectious diseases [1].

Anti-cancer Activity of Scopoletin: Chemo-therapy with cisplatin in cholangiocarcinoma produces adverse effects and leads to resistance development by tumors, thus scopoletin is given with cisplatin, which resulted in a dose-dependent reduction of cell viability for cholangiocarcinoma cells. The combination of these agents inhibited the proliferation of cells significantly more than single agent either. Combination indices reflect additive cytotoxic effect, leading to >2 times dose reduction for each agent. Both the cell cycle arrest (G0/G1) and apoptosis induction underling the enhanced cytotoxicity for the combination. Besides, single agent conferred cell cycle arresting and apoptotic effects in cholangiocarcinoma cells. By contrast, non-cancer cells were less affected with a combination. This treatment suggests that cisplatin and scopoletin combination may bring positive significance in cholangiocarcinoma treatment [10].

Scopoletin may have several pharmacological effects that extend from the enhancement of phagocytosis and immunomodulatory effects to prevention and treatment of cancer progression and metastasis. It might be considered in management of other diseases such as some autoimmune disorder, GvHD, pelvic organ prolapses, Sjogren's syndrome, and cystic fibrosis [11].

Breast Cancer: *M. citrifolia* leaf extract had a scopoletin content of 0.58% (w/w) and could inhibit viability and migration in the MCF‑7 cell. Therefore, the extract has the potential for development as an anticancer agent for breast cancer [12].

Prostate Cancer: Scopoletin exhibits potent anticancer activity by inducing apoptosis, cell cycle arrest, and downregulating the expression of cyclin D1 levels in human prostate cancer (LNCaP) cells, thus making it an important natural product for the development of chemotherapeutic agents against prostate cancers and paving a way to elucidate further the mechanism of its action in order to make it more efficient against human prostate cancer [13].

Anticonvulsant Activity of Scopoletin: Scopoletin, which was reported earlier as anti-convulsant tentatively, supports the anticonvulsant activity of the plant extract, which may be due to scopoletin alone or is a result of synergy of many compounds in the fraction in which scopoletin is the major constituent. In order to further validate our claim, the isolated scopoletin was subjected to GABA-T inhibitory assay. Scopoletin was found to significantly inhibit the enzyme [14].

Anti-cholinesterase Activity of Scopoletin: In the anti-AChE assay, scopoletin reported a moderate activity compared to galanthamine. This assay measures the inhibition activity against AChE, which is the key enzyme in the hydrolysis of acetylcholine that is responsible for muscle and organ relaxations. Acetylcholinesterase inhibitors are therefore used medicinally to treat myasthenia gravis to increase neuromuscular transmission and to treat Alzheimer's disease (deficiency in the production of acetylcholine) [15].

Anti-depressant Activity of Scopoletin: The coumarinscopoletin produced a specific antidepressant-like effect in the tail suspension test, an animal model predictive of antidepressant activity, and was also able to reverse a depressant-like behaviour induced by acute immobility stress. In addition, this work provides evidence that the antidepressant-like effect of scopoletin in the tail suspension testis dependent on the interaction with the serotonergic (5-HT2A/2Creceptors), noradrenergic (α1- and α2-adrenoceptor) and dopaminergic (D1 and D2 receptors) systems. Results suggest thatscopoletin shares with established antidepressants some pharmacological effects, at the preclinical level [16].

Anti-diabetic Activity of Scopoletin: The potential anti-diabetic activity of scopoletin via its inhibitory effect on α-glucosidase and α-amylase.

Furthermore, scopoletin may help the suppression of increased postprandial blood glucose levels. Thus, we suggest that scopoletin could be used as a nutraceutical agent for patients with diabetes [17].

New findings also suggest that the scopoletin increases glucose uptake in 3T3-L1 adipocytes via activation of the PI3K/Akt and AMPK pathways. This activation was verified through the use of the PI3K inhibitor wortmannin, and the AMPK inhibitor Compound C. Finding suggests that scopoletin may be developed as a potential anti-diabetic compound for the stimulation of glucose uptake and improvement of insulin sensitivity [18].

Antidopaminergic and Antiadrenergic Activity of Scopoletin: Methanolic extract of *M. citrifolia* (MMC) showed a biphasic effect on dopaminergic system, that is, antidopaminergic effect at a lower dose (<40 mg/mL) and dopaminergic agonistic effect at a higher dose (>60 mg/mL) in the isolated rat vas deferens preparation. Additionally, MMC (<30 mg/mL) showed the antiadrenergic activity in the rat vas deferens. Furthermore, antidopaminergic and antiadrenergic activities of scopoletin (<200 μg/mL) and rutin hydrate (<312.6 μg/mL), respectively, have been established. It has been postulated that the bioactive principles of noni, scopoletin, and rutin, could be responsible for the antidopaminergic and antiadrenergic activities of MMC. However, the mechanism of high dose contractile response of MMC on rat vas deferens could not be explained in the present study [19].

Anti-fungal activity of Scopoletin: The antifungal activity of seed kernel extract from *M. azedarach* has been reported in previous publications, and three compounds responsible for this activity have been isolated. The hydroxycoumarin scopoletin obtained from the same extract, showing antifungal effect but, when combined with the other active compounds, a greatly unexpected enhancement of the activity [20].

One more finding also shows that the scopoletin isolated here from *Mitracarpus frigidus* is a coumarin with antifungal activity against a clinically relevant fungal species, the multi-drug-resistant *C. tropicalis* ATCCR 28707 strain. Data also provided the first insights to understand the events of microbial growth inhibition and death induced by *M. frigidus*-isolated scopoletin, which acts by interfering with the synthesis of essential fungal cell components and is able to disrupt both cell wall and plasma membrane. Moreover, scopoletin affects the growth rate of preformed *C. tropicalis* biofilms as well as its stages of formation and proliferation. Thus, the present data encourages the development of drugs based on plant isolated-scopoletin to treat candidiasis caused by C. tropicalis [21].

Anti-hepatosteatosis& Anti-obesity Activity of Scopoletin: Scopoletin can prevent alcoholic hepatosteatosis *via* coordinated regulation of the WAT– liver axis during lipid metabolism and inflammation. Scopoletin up-regulated adiponectin-AMPK activation and the expression of PPARa target genes, which led to lipid catabolism and inhibition of lipid deposition. In addition, scopoletin significantly suppressed the alcohol-induced TLR4-MyD88-dependent and -independent pathways, which may play an important role in the prevention of alcoholic inflammation [22].

A low dose of scopoletin (0.01%, w/w) attenuated NAFLD and prevented hepatic fibrosis development in diet-induced obese mice. Supplementation of scopoletin in the HF-induced model of NAFLD resulted in lower serum and hepatic lipid contents, amelioration of insulin resistance and inflammation, which may explain the hepatic transcriptional analysis and gene expression. Accordingly, these findings suggest scopoletin could be safely used as a functional food resource for NAFLD [23].

Antihypertensive Activity of Scopoletin: It has been reported that *Morinda citrifolia* is able to reduce hypertension through the activity of ACE inhibitor and antioxidant activity of phenolic compounds including scopoletin and rutin that could capture free radicals [24].

Antihyperuricemic Activity of Scopoletin: The therapeutic mechanisms of dual urate-lowering effects of Sco-Ms in hyperuricemic mice were demonstrated for the first time in this study. A sustained and stable mice model of hyperuricemia was established. So showed a weak urate-lowering effect after continuous oral administration of Sco. With higher drug distribution of Sco, Sco-Ms

exhibited better antihyperuricemic effect in hyperuricemic mice than Sco. Sco showed inhibitory effect neither on the serum nor the hepatic XOD activity, while Sco- Ms could significantly reduce the production of uric acid through inhibiting the activity of hepatic XOD. Moreover, due to the more potent modulation on the expression levels of URAT1, GLUT9 and OAT1, Sco-Ms improved the uricosuric effect of Sco. Findings indicated that Sco-Ms was a promising approach for Sco to treat hyperuricemia [25].

Anti-inflammatory Activity of Scopoletin: In the 5-LOX assay, scopoletin displayed potent enzyme inhibition, which was fiftyfold more than nordihydroguaiaretic acid. According to the 5-LOX enzyme inhibition activity measurement, scopoletin displays good enzyme inhibition activity. A combination of anti-inflammatory and antioxidant assays constitutes a good indication on the potential anti-inflammatory activity of a drug, as inhibition of the lipoxygenases is due to the reaction of the inhibitor with free radicals generated at the active site of the enzyme. This assay measures the inhibitory activity against the 5-LOX enzyme, which is the key enzyme in the metabolism of arachidonic acid that is responsible for the formation of leukotrienes which play a pivotal role in the pathophysiology of chronic inflammatory and allergic diseases [15].

Scopoletin (0.001% and 0.005%) can prevent alcoholic hepatosteatosis *via* coordinated regulation of the WAT– liver axis during lipid metabolism and inflammation. Scopoletin up-regulated adiponectin-AMPK activation and the expression of PPARa target genes, which led to lipid catabolism and inhibition of lipid deposition. In addition, scopoletin significantly suppressed the alcohol-induced TLR4-MyD88-dependent and -independent pathways, which may play an important role in the prevention of alcoholic inflammation [22].

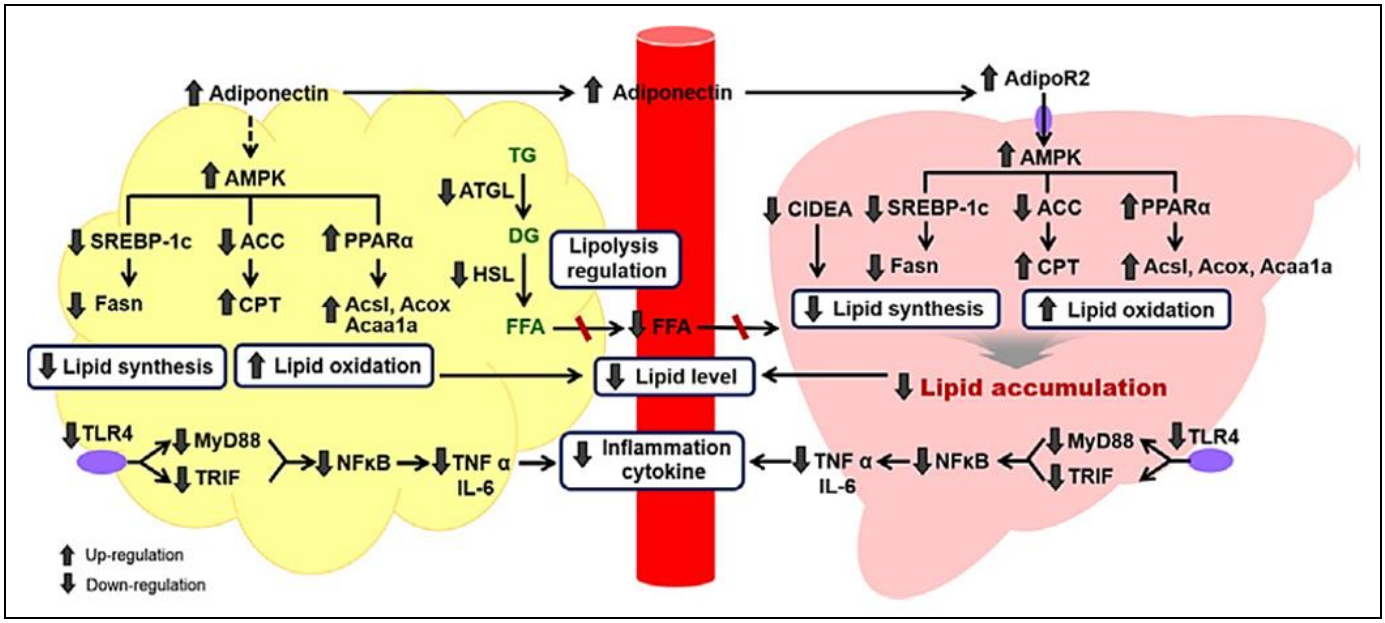

FIG. 4: SCOPOLETIN ATTENUATED ALCOHOL INDUCED LIPID DYSMETABOLISM AND INFLAMMATION

Scopoletin possesses a remarkable anti-inflammatory activity in both croton oil- and carrageenan-induced inflammatory models, possibly originating from its inhibitory activities on PGE2 and TNF-α overproduction and neutrophil infiltration [26]. Scopoletin and quercetin were isolated from non-fruit puree as potentially beneficial components related to anti-inflammatory and anti-cancer activities. In the anti-inflammatory bioassay, a synergistic relationship between these two components (at ~5 μMeach) at the same ratio they are present in the active extract of noni puree. The combined actions of these compounds likely involve multiple mechanisms of biological effect [27]. Scopoletin can regulate the inflammatory response induced by PMA plus A23187 in mast cells. Scopoletin affects the expression of inflammatory cytokines by regulating the IκB/NF-κB signal cascade. Overall, our results suggest that scopoletin is a specific inhibitor of the production

of inflammatory cytokines in HMC-1 cells, and this inhibition might explain its beneficial effect in the treatment of chronic inflammatory diseases [28].

Anti-microbial Activity of Scopoletin: The scopoletin isolated from stem bark lipophilic extracts of *L. lucidus* showed significant antibacterial properties in a similar manner; from this action, morphological changes could be observed on bacterial cells after treating with compounds. The lipophilic extracts showed pronounced from several plants in the genus Lasianthus (Rubiaceae) have inhibited pathogenic bacteria, especially in *P. aeruginosa* and which one related to traditional infectious diseases. Thus, these authors have explained that scopoletin seems to be an effective antimicrobial as proved by the bioassays [1].

Antimigratory Activity of Scopoletin: This study revealed that *M. citrifolia* leaf extract had a scopoletin content of 0.58% (w/w) and could inhibit viability, and it showed an anti-migratory effect on MCF‑7 cells [12].

Antioxidant Activity of Scopoletin: Scopoletin which passes the Lipinsky rule, for the possible lead compound in drug discovery and, in agreement with its potent antioxidant power, good anti-inflammatory and moderate anti-acetyl-cholinesterase activity demonstrated in this study might be of value for the treatment of various diseases emerging from oxidative stress [15].

Scopoletin, isolated from *Sinomonium acutum*, scavenged xanthine/xanthine oxidase-generated superoxide anion in a dose-dependent manner without directly affecting xanthine oxidase activity. Apart from specific enzymes, such as SOD, only a few compounds can react with superoxide anions. Thus, scopoletin may be of use in preventing superoxide anion-induced damage *in-vivo*. This simple coumarin inhibits prostaglandin synthetase, and its use as a topical anti-inflammatory application has been reported. The antioxidant properties of scopoletin had not previously been investigated. The ability of scopoletin to scavenge superoxide anion, demonstrated in this study, may promise its further usage in slowing or preventing diseased conditions related to oxidative damage [29]. The effects of scopoletin were compared with that of PTU; although both appeared to be equipotent in inhibiting thyroid functions, scopoletin also inhibited hepatic LPO indicating an antioxidative nature. Scopoletin was also able to enhance the activity of endogenous antioxidants, including SOD, CAT, and GSH [30].

Scopoletin had higher superoxide anion radical scavenging activity. Scopoletin was an effective OH-radical scavenger in a concentration-dependent manner. There was a significant decrease in the concentration of OH radicals due to the scavenging capacity at all scopoletin concentrations. The scavenging effect of scopoletin and standards decreased in the order: scopoletin< α-tocopherol, which was at the concentration of 45 μg/mL, respectively. Scopoletin may play an important role in regulating free radicals generated *via* various body metabolic activities such as mitochondrial transport of long-chain free fatty acids and cytochrome-p450 transport chain. These data suggest that Scopoletin has the propensity to modulate endogenous oxidative stress and may be an effective nutraceutical to abrogate oxidative stress in the body [31].

Anti-proliferative Activity of Scopoletin: Scopoletin showed reduced anti-proliferative effects on all cancer cell lines. Scopoletin had a slight inhibitory effect on all tested cells [32].

Anti-termite Activity of Scopoletin: Scopoletin, quercetin, and stigmasterol from the ethyl acetate fraction of *P. javanicum* Burm. f. leaf extract by bioassay-guided fractionation. The anti-termite activities of scopoletin, quercetin, and stigmasterol against *C. formosanus* Shiraki and found that scopoletin showed the highest activity among the three compounds. In order to investigate the SAR of the methoxy and hydroxy groups at the C-6 and C-7 positions of the coumarin skeleton, respectively, they synthesized several coumarin derivatives whose chemical structures are similar to scopoletin.The comparison of termite mortalities for scopoletin and coumarin derivatives (2–10) suggested that scopoletin showed the strongest termiticidal activity among the 10 compounds tested, followed by 3, 7, and 8, in that order. The other compounds showed weak activity. Further, all compounds except compound 9 showed antifeedant activity. These results suggest that scopoletin and

other coumarin derivatives whose chemical structures are similar to scopoletin might be useful for termite control agents, because they are abundant in plants or synthesized using well-established procedures [33].

Anti-thyroid Activity of Scopoletin: In the present study, both T3 and T4 levels were decreased by scopoletin, which suggests that the compound may be acting on the thyroid gland (the only site of T4 synthesis) as well as at the level of the peripheral conversion of T4 to T3 (the main source of T3 generation).

Since thyroid hormones are also gluconeogenic as well as glycogenolytic in nature, the changes in serum glucose concentrations could be the result of scopoletin-induced alterations in the status of thyroid functions in animals. Whatever may be the mode of action, from the present findings, it appears that scopoletin has the potential to ameliorate hyperthyroid as well as hyperglycaemic conditions without any hepatotoxic effects [30].

Anti-tubercular Activity of Scopoletin: Compounds from *Morinda citrifolia* Lin (noni) fruit such as flavonoid, scopoletin, anthraquinone, and alkaloid have anti-tuberculosis activity against *M. tuberculosis* (H37RV).

The crude extracts of noni fruit were the most active compound compared the other group against *M. tuberculosis* (H37RV) [34].

Anti-tumor Activity of Scopoletin: Scopoletin possesses strong anti-angiogenesis activity in animal models. Further, the inhibitory effect of scopoletin was exploited to demonstrate its remarkable antitumorigenic activity in a human tumor xenograft model. Histological and immune histochemical analysis of excised tumors revealed that scopoletin displayed drastic suppression of tumor vasculature [6]. Scopoletin induced cell proliferation on normal T lymphocytes; this stimulatory action was found to be due to the interaction with kinase C (PKC) protein. These results indicate that scopoletin could be a potential antitumoral compound to be used for cancer treatment [35].

Scopoletin might serve as a lead compound for drug development and would find its way into the clinics, is supported by the favourable activity against tumors expressing well-known drug resistance mechanisms, although RAS mutations and NF-_B may hamper the effectiveness of scopoletin [36].

Twenty scopoletin derivatives were developed by a systematic combinatorial chemical approach, and their chemical structures were confirmed by MS, IR, 1H NMR spectra, and elemental analysis. Primary screening against mammary (MCF-7 and MDA-MB 231) and colon (HT-29) carcinoma cells indicated that five compounds (8d, 8g, 8j, 11b, and 11g) displayed high antitumor potencies with IC_{50} values. Moreover, the most promising compound 11 g was more active than 5-fluorouracil. These results clearly indicated that the modification of the scopoletin structure could greatly increase its antitumor activity *in-vitro* [37].

A series of hybrids of scopoletin and substituted cinnamic acid were designed, synthesized, and evaluated *in-vitro* and *in-vivo* against five human tumor cell lines [MCF-7, MDA-MB-231, A549, HCT-116, and HeLa] with doxorubicin as the positive control. Compounds 17a, 17b, 17c, and 17g exhibited potent cytotoxic activity. Especially, compound 17b displayed broad-spectrum activity with IC_{50} values ranging from 0.249 μM to 0.684 μM. Moreover, in a preliminary pharmacological study, 17b not only remarkably induced cellular apoptosis but also clearly induced A549 cells cycle arrest at S phase. An *in-vivo* study showed that 17b significantly suppressed tumor growth in a dose-dependent manner without causing the loss of the mean body weight of mice, which was superior to doxorubicin. These preliminary results indicate that 17b is an optimal anti-tumor leading compound and merit further structural modification [38].

Hepatoprotective Activity of Scopoletin: Scopoletin protects hepatocytes from CCI4-induced toxicity by maintaining the GSH content, the activity of SOD, and inhibiting the production of MDA as a result of its antioxidation and free radical-scavenging effect. Scopoletin is a well-known, simple coumarin that is widely distributed in the various families of the Angiosperms, especially Solanaceae, Convolvulaceae, Composite, *etc.,* but has never been previously isolated from *S. lyratum*. Its hepatoprotective activity and the

mechanism of action are for the first time reported in the present communication [39].

Neuroprotective Activity of Scopoletin: The neuroprotective potential of scopoletin was found to be 69% against Aβ42-induced neurotoxicity and 73% against H_2O_2-induced cytotoxicity in PC12 cell culture at 40 µM final concentration. At the same concentration, scopoletin inhibited Aβ42 fibril formation up to 57%. The IC_{50} concentration for AChE and BuChE enzyme inhibition by scopoletin was 5.34 and 9.11 µM, respectively. The ant aggregation and enzyme inhibition results were complemented with strong molecular interactions of scopoletin with target proteins validated by in silico molecular docking analysis. Based on this study, it can be concluded that scopoletin can be used as a lead for the amelioration of symptoms and disease-modifying effects in AD [5].

Scopoletin plays crucial role in neuroprotection by maintaining the antioxidant status. This may critically support neuronal cell survival in the face of H_2O_2-induced neurotoxicity. Such action may prevent AD *via* reducing toxic Ab shedding, although it remains unclear exactly how these compounds ameliorate the neurotoxicity. The findings suggest that these polyphenolic compounds are potential candidates for prevention and/or treatment of neurodegeneration in the future [40].

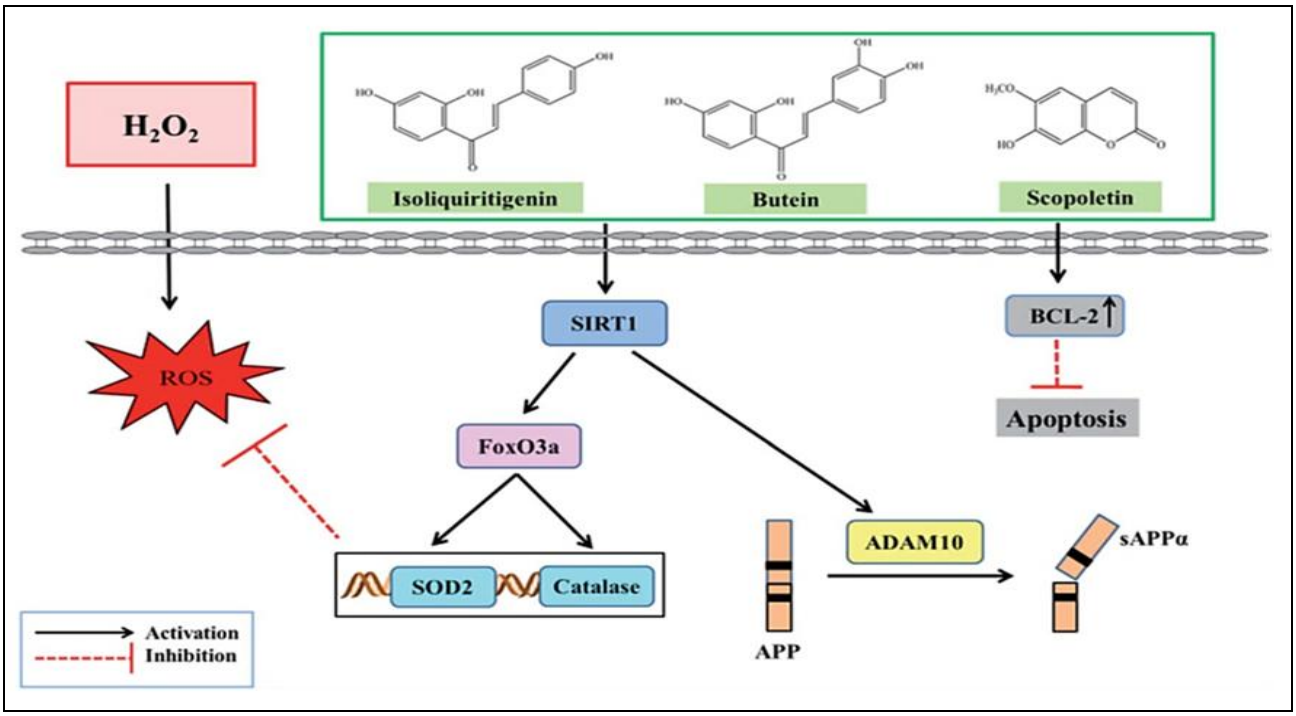

FIG. 5: POSSIBLE NEUROPROTECTIVE EFFECTS OF BUTEIN, ISOLIQUIRITIGENIN, AND SCOPOLETIN ON NEURONAL CELLS

Scopoletin inhibited Bid and Bax, and suppressed caspase-9 cleavage by caspase-9 activation. Thus, the expression of cleaved caspase-3 and the expression of cleaved PARP were suppressed. This indicates that scopoletin inhibits caspase-3 by inhibiting Bid, Bax, and caspase-9 and reduces PARP cleaved by caspase-3. Apoptosis has extrinsic and intrinsic pathways. Mitochondria play an important role in intrinsic pathways apoptosis. Cytochrome c exits between the apoptotic pores formed by Bax, bak, *etc.*, migrates to the cytoplasm, and binds to apaf1 and caspase-9 to form apoptosomes. We have experimentally confirmed that scopoletin has an anti-apoptotic effect through the intrinsic pathway. In alcohol-induced apoptosis, scopoletin initiates the anti-apoptosis effect by inhibiting the Bid that links extrinsic and intrinsic pathway apoptosis. Also, by inhibiting Bax, apoptotic pore formation is suppressed, and caspase-9 activity is suppressed to suppress apoptosome formation. It inhibits the activity of caspase-9 and inhibits the activity of caspase-3 by the sequential cascade. These results suggest that down-regulation of Bid, Bax, and

caspase-9 activation by scopoletin suppress caspase-3 activation, cleavage of PARP, and finally inhibit mitochondrial apoptosis pathways. This shows the protective mechanism of scopoletin on alcohol-induced apoptosis in primary hippocampal neurons. This data was obtained from *in-vitro* experiments, and it is necessary to examine the scopoletin effect on alcohol-induced neurotoxicity rodent models. Nevertheless, the study presents novel evidence that scopoletin can be applied as a candidate for neuroprotection [41].

UPEI-400, a chemical combination of two naturally occurring compounds, LA and scopoletin, produced dose-dependent neuroprotection against neuronal cell death as observed in a previously validated, novel model of ischemia-reperfusion (I/R). The results demonstrated that UPEI-400 produced neuroprotection following 5.5 h of reperfusion in a model of focal ischemia, which is restricted to the prefrontal cerebralcortex. Further, the dose of UPEI-400 required to produce significant neuroprotection (0.001 mg/kg) was 1000-fold less compared to the dose required for scopoletin alone (1.0 mg/kg), and 5000-fold less compared to the optimal neuroprotective dose of LA alone, observed inour lab previously. Also, the optimal dose of UPEI-400 produced significant neuroprotection when administered 15 min prior to the start of reperfusion and when administered 30, 90, and 150 min following the onset of reperfusion. Clinically, the paradigm of administering UPEI-400 during and/or following the occlusion was to mimic the clinical situation in which therapy would be administered at the time a patient presents to a hospital following the onset of a stroke or following administration of thrombolytic therapy (to prevent reperfusion injury). These results also suggest that UPEI-400 provides neuroprotection against reperfusion injury [42].

Role of Scopoletin in Esophagitis and Gastric Ulcer: Aqueous extract of dried Noni fruit as well as its biomarker: scopoletin may be beneficial as a potential preventive and therapeutic agent for gastro-esophageal inflammation, mainly through its antisecretory and prokinetic activities, including its ability to enhance the mucosal defensive mechanisms through suppression of serotonin, free radicals, and cytokine-mediated inflammation. Owing to the lack of prokinetic and anti-inflammatory activities of currently standard antiulcer agents, the regimen of combining an aqueous Noni fruit extract and H2 receptor antagonists or proton pump inhibitors may be beneficial in the treatment of reflux esophagitis and peptic ulcer. Additionally, scopoletin might be one of the biomarker constituents for quality assessment of Noni fruit products used to treat upper gastrointestinal disorders [43].

Role of Scopoletin in Neurological Disorders: Coumarin scopoletin as reversible and selective MAO-B inhibitor. It is approximately 3.5 times more selective towards MAO-B than for MAO-A. Docking studies revealed insights about the binding mode of scopoletin with both the isoforms of MAO enzymes. We also proved scopoletin affects the metabolism of endogenous brain amines, mainly dopamine.

To summarize: (a) scopoletin crosses the blood-brain barrier, (b) it is a partially selective MAO B inhibitor, and (c) it markedly affects dopamine metabolism in striatum [44].

CONCLUSION: In summary, this review demonstrates that Scopoletin (7-hydroxy-6-methoxy coumarin) is isolated from many plants. Scopoletin has been found in many plants such as *Morinda citrifolia*, *Aegle marmelos*, Erycibe *obtusifolia Benth*, *Lasianthus lucidus* Blume, *Melia azedarach* L., *Sinomonium acutum*, Convolvulus prostratus, and *Solanum lyratum*, etc. which all possess various medicinal properties which might be helpful in treating various disease. Scopoletin can be synthesized from the 2, 4, 5-trimethoxy-benzaldehyde. From the literature review, it is concluded that scopoletin a phenolic coumarin which is present in various plant and species have numbers of pharmacological activities. Its various pharmacological activities have been reported through a number of investigations. Scopoletin plays an important role in treating various diseases such as Alzheimer's disease, anxiety, cancer, depression, epilepsy, esophagitis, diabetes, gastric ulcer, hypertension, hyperuricemia, inflammation, obesity, rheumatoid arthritis, thyroid, tuberculosis, and tumor. Due to its anti-angiogenic, antibacterial, anti-fungal, anticholinesterase, anti-dopaminergic, antiadrenergic, antimicrobial, antioxidant, anti-proliferative, hepatoprotective and neuroprotective

properties, scopoletin has the potential to be helpful in the treatment of other diseases as well, which need to be developed further.

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