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Systematic Review on Nobiletin a Phyto-Constituent Having Potential to Prevent and Manage Multiple Ailments

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1. Abstract

Nobiletin is an abundant phytoconstituent having multiple pharmacological activities. Various citrus species like orange (Citrus sinensis), lemon (Citrus limon), grapefruit (Citrus paradisi) and tangerine (Citrus tangirina) having flavanones, flavones, flavon aglycon, and Polymethoxyflavones (Nobiletin & Tangeretin). Nobiletin (HMF); Hexamethoxyflavone {2-(3, 4)-dimethoxyphenyl) -5,6,7,8-tetramethoxychromen-4-one}is extracted from non-edible orange peel rich in polymethoxyflavones (PMFs). Many are suggesting Nobiletin as chemo-sensitizing agent induces nuclear retention of tumor suppressor protein and Tyrosinase inhibitor, inhibiting hepatitis B virus replication. It is also proposed that 2-aryl-4H-chromen-4-one derivative may be effective in Chikungunya Virus, and other suggested multiple activity. Citrus species are traditionally used in Ayurveda as immune modulator which is effective in viral disease because of their antioxidant properties. To study the ability as drug of an independent phyto-active Nobiletin (HMF) is under consideration, HMF is lipophilic in nature, its physiochemical properties may enhance by increasing water solubility for more bioavailable, and prospective as therapeutic agent or as broad-spectrum antiviral.

2. Introduction

Naturally occurring Polymethoxy flavones (PMFs) indigenously present in various citrus species [1]. Citrus sinensis peel extract contain PMFs [2] among of them Nobiletin (HMF); Hexa-methoxy flavone {2-(3,4)-dimethoxyphenyl)-5,6,7,8-tetramethoxychromen-4-one and other constituents are extracted by solvent extraction [3] or by supercritical fluid extraction [4]. crystal structure of nobiletin comprises of chromene and aren rings are in same plane, chirality is indicated by their covalent bond rotation, HMF is lipophilic and absorbed by cell membrane permeation. Nobiletine having multiple pharmacodynamic activities various study suggested like anticancer, anti-inflammation, antioxidant, anti-insulin resistance, anti-osteoclastogenesis, neuroprotective etc [5].

3. Chemistry of Nobiletin

A flavonoid must contain 15-carbon Skelton with three ring system and multiple hydroxy groups/polyphenols. in (Figure 1): a three-ring system structure containing multiple methoxy groups is a natural flavonoid Nobiletin [6]. (Figure 2): Substitution at chromone ring system have different pharmacodynamic action i.e. R1: Phenylmethyl group [preferably hydroxylated] (neuroprotective activity). R2: Dithiocarbamate, coupled to a 6-Cl substituent (antitumor activity), Benzoyl substituent (enhanced antioxidant activity), and Heterocyclic thioether or cyclic tertiary amine (improved antitumor activity). R7: 7, 8-Dihydroxy substituent (essential for antioxidant activity) [7]. Polymethoxy flavones (PMF) in (Figure 3): polymethoxy flavones skeleton where R1 to R5 = OMe, R1 and R2 = OMe.

3.1. Natural Source of Pmfs and Nobiletin

Orange, lemon, grapefruit and tengerine having flavanones, flavones, flavon aglycon, and Polymethoxyflavones (Nobiletin & Tangeretin), they are available as source of flavonoids [8]. Potential nutritional citrus fruits having functional and nutritional value and their pericarp (peel) is a waste containing functional polymethoxy flavone and Nobiletin [2].

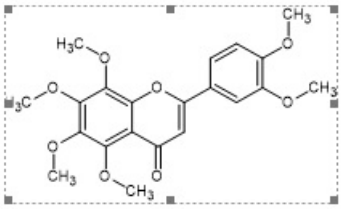

Figure 1: 2-(3,4-dimethoxyphenyl)-5,6,7,8-tetramethoxychromen-4-one.

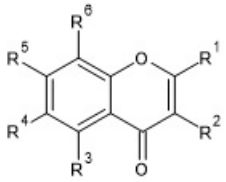

Figure 2: chromen-4-one (chromone).

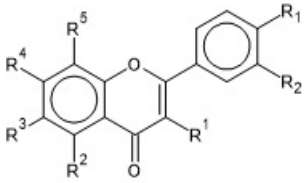

Figure 3: Polymethoxy flavones R^1 to R^5 and R_1, R_2 = H or OMe.

3.2. Methods of Extraction

Polymethoxyflavones from Citri reticulatae pricarpium by Supercritical Fluid Extraction (SFE) obtain maximum yield of crude extract 1.91%, maximum concentration of PMFs 17.03%, and maximum yield of PMFs 2.08 mg/g. SFE condition are 30 Mpa, 60°C, 1.5 hr. with ethanol [4]. Supercritical extraction with ethanol as modifier in different concentration 0-20%, 4.8-13% (flow rate 0.15 to 0.45 ml/min) at 30 Mpa, 80 C, CO2 flowrate 3 ml/min, Soxhlet extraction with 85% aqueous ethanol for 4 hr. for PMFs extraction from Citrus depressa Hayata [9]. Citrus Unshiu peel extracted by supercritical fluid extraction in condition 333K, CO2-ethanol flowrate 0.026 mol/min, at 30Mpa pressure [10]. PMFs extracted from Citrus pomaces by subcritical water (SCW) extraction at 200°C, 1.4 MPa, for 60 min [11].

3.3. Physiochemical Parameter

Nobiletin have molecular formula C21H22O8, CAS no 478-01-3, molecular weight 402.4, white to off white solid, soluble in methanol, and stability stable over (-20°C) [12]. Specific dosing, safety and efficacy data, interaction data, adverse reaction, toxicological data are still not available [13].

4. Pharmacological Activity

Nobiletin as food supplement and an antioxidant may help in circadian cycle [14].

4.1. Multi-Drug Resistance (MDR)

It enhances the effect of paclitaxel in cancer cell (Tumor) by inhibiting P-glycoprotein or by inhibiting AKT/ERK/Nrf2 pathway consider as MDR tumor reversal agent [15].

4.2. Leukemia

Exhibit cytolytic activity in human leukemic natural killer cell line KHYG-1, elevate to cytotoxic protein granzyme B and cytokine interferon-γ by nuclear retention of NF-kB transcription factor [16].

4.3. Hepatitis B Virus (HBV)

An antigen (HBsAg) is responsible for the HBV infection caused cirrhosis and hepatocellular carcinoma, study suggesting nobiletin as less toxic and effective antiviral agent determined in HepG2.2.15 and HepG2-NTCP cells [17].

4.4. Anaplastic Thyroid Cancer

Study suggested it decreases viability of normal thyroid and ATC cell line (T235, T238) by arresting cell cycle at 100 μM [18].

4.5. Pmfs in Newhall Naval Orange (Citrus Synapsis)

Successive extraction of Newhall orange peel 95% ethanol by petroleum ether, ethyl acetate, and water extract by liquid-liquid extraction suggested ethyl acetate have significant activity as antioxidants, anti-bacterial, and tyrosinase inhibition [19].

4.6. Obesity

Study suggested activation of AMPK enhance LXRα transcription which increase transcription of ABCA1 and ABCG1 for HDL biogenesis and increased their expression [20]. Increased phosphorylation of AMP-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC) in primary mouse hepatocytes [21].

4.7. Ovarian Cancer

It suppresses ovarian cancer cell proliferation, induced DNA damage, and lead to apoptosis by increasing the cleaved Poly (ADP-ribose) polymerase enzyme (PARP) level [22].

4.8. Random Pattern Skin Flap

Study suggested nobiletin mitigate oxidative stress by augmenting superoxide dismutase, reducing malondialdehyde, and increase vascular endothelial growth factor expression and also increase blood flow to improvise skin flap necrosis [23].

4.9. Alzheimer's and Parkinson's disease

It has been proven that it improved motor and cognitive deficits in PD and pathophysiological improvement in amyloid-β peptide (Aβ)-pathology, oxidative stress, and hyperphosphorylation of tau [24, 25], improved memory by enhancing cAMP/protein kinase A/extracellular signal regulated kinase/cAMP response element binding protein signaling [26].

4.10. Anti-Hypertensive

N-nitro-L-arginine methyl ester (L-NAME) induced hypertension in

mice investigated effect of Nobiletin. Outcome of the study suggested that it decrease oxidative stress, restore abnormality of plasma NOx and protein expression of eNOS, Nrf-2, and HO-1 [27]. Citrus unshiu peel (CUP) extract containing Nobiletin have anticontractile activity, and also exhibits relaxation in mesenteric arteries through the calcium-eNOS pathway in endothelium [28].

4.11. Osteoarthritis

Recent study suggested its chondroprotective ability to reduce development of osteoarthritis through inhibiting proinflammatory cytokines expression and reducing expression of interleukin-21, in MH7A fibroblast-like synoviocytes (FLS). Alternative mechanism proposed to increasing expression of interleukin-6, tumor necrosis factor-α (TNF-α), and high-mobility group box 1 (HMGB1). It has also reduced mitochondrial membrane potential through its own mechanism [29].

4.12. Tyrosinase Inhibitors

Study against kojic acid shows IC50 value of 131.92 ± 1.75 in in-vitro and in-silico study [30].

4.13. Anti-Tuberculosis

Its antibacterial activity may be related to the methoxy or hydroxy group, suggesting nobiletin as a potent inhibitor of growth of M. aurum and M. bovis BCG and interfere pump activity of M. aurum and M. smegmatis consider as candidate for TB treatment [31].

4.14. Hepatoprotective

Study suggested nobiletine induced autophagy by increasing SIRT-1 and FOXO3a expression, and decrease AKT phosphorylation [32].

4.15. Cardioprotective

In-vitro study shown that it exhibits cardioprotective activity against ischemia/reperfusion (I/R) injury, and myocardial hypoxia/reoxygenation (H/R) injury, improve cell viability inH9c2 cells, also inhibit to reactive oxygen species malondialdehyde, cell apoptosis, and levels of pro-inflammatory factors [33].

4.16. Metastatic Prostate Cancer

A combination of nobiletin and sorafenib inhibit viability of PC-3 cells. It causes apoptotic cell death and inhibit G0/G1 cell cycle phase regulated by Bax, Rb1, and CDKN1a levels [34].

4.17. Lung tumorigenesis

Tumor volume comparatively reduced by metabolite of nobiletin, 3'-demethylnobiletin, 4'-demethylnobiletin and 3',4'-didemethylnobiletine. It had caused significant cell cycle arrest, apoptosis, modulation in multiple associated protein with proliferation and cell death [35].

4.18. Antiviral Against RSV

SFE extract of Citrus reticulata exhibit in vitro anti respiratory syncytial virus (RSV) activity, which contain tangertin and nobiletin as polymethoxy flavonoids, and also exhibit cytopathic effect (CPE) reduction assay [36].

4.19. Antigen-Specific Immune Response

Its increased (OVA) specific IL-4 and IL-10, shows higher level of OVA-specific IgE, IgG, and IgG 1production, and its ability to enhance antigen presentation of bone merrow -derived dendritic cells [37].

4.20. Memory

It has been reported that it suppresses the microglial activation, secretion of proinflammatory mediators such as COX-2, IL-1β, TNF-α, and iNOS. It is also proposed that the stimulation of lipopolysaccharide (LPS) is reduced thereby diminishing the secretion of the proinflammatory cytokines in BV-2 microglia cells via modulating different pathways such as MAPKs, PI3K/AKT, and NF-ϰB signal transduction mechanisms [38].

4.21. Ulcerative Colitis

Flavonoids especially naringenin, nobiletin and hesperetin are reported to lessened body weight loss and the shortness of colon along with reduction in DAI score, and significantly increased claudin-2, occludin and zona occludens-1 (ZO-1) expression. It is also reported that these flavonoids significantly increased trans-epithelial electric resistance.and occludin and ZO-1 expression in LPS-damaged epithelial monolayers system. Whereas, significantly decreased the permeability [39].

4.22. Anti-Chikungunya Virus

One of the studies suggested some synthetic 2-aryl-4H-chromen-4-one derivative exhibits anti-chikungunya activity in Vero cell culture by CPE reduction assay [40].

5. Conclusion

Emerging Infectious disease are going pandemic like chikungunya, zika, Ebola, Avian influenza/bird flu, MERS-CoV, H1N1 Influenza A (Swine Flu), H5N1 Influenza A (Avian Influenza/Bird Flu), SARS-CoV, DEN I-IV (Dengue fever) [41], and existing pandemic SARS-nCoV, chromone derivative may be effective in prevention of viral infection. Nobiletin having a functional chromone pharmacophore with multiple methoxy side chain or aryl substitution may exist antihypertensive, hepatoprotective, neuroprotective, reduce osteoarthritis and its antiviral effect. In current pandemic situation nobiletin may considered as a natural antiviral agent for combat infectious disease and support to other organ impairment occurred due to infectious disease. Nobiletin may be considered as protective remedy. However, there is a scope for method development for extraction and isolation of nobiletin in commercial scale.

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