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Review Article

Nobiletin as a Neuroprotective Agent: Therapeutic Potential and Formulation Strategies for Alzheimer's and Related Disorders

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Abstract

Objectives: The purpose of this review is to investigate the neuroprotective properties of the dietary polymethoxy flavone nobiletin (NOB), specifically in connection to Alzheimer's disease and other neurological conditions. To enhance the compound's medicinal effectiveness, it also examines its chemical properties, modes of action, and the latest developments in formulation techniques.

Data Sources: From 2000 to 2024, pertinent scientific literature on pharmacological investigations, formulation developments, and preclinical assessments of nobiletin was compiled from databases including PubMed, ScienceDirect, Google Scholar, and Web of Science.

Study selection: Research was chosen based on its experimental significance for the pharmacodynamics, bioavailability, neuroprotective effectiveness, and formulation technologies of nobiletin. Pharmacokinetic studies, patents, and in vitro and in vivo research were all included.

Summary of Contents: Citrus peels are the primary source of nobiletin, which has potent anti-inflammatory, antioxidant, anti-cancer, and neuroprotective qualities. Problems including low bioavailability and poor water solubility have prompted the creation of sophisticated formulations such as solid dispersions, micelles, and nanoemulsions. Its pharmacokinetic profile and therapeutic potential have been enhanced by these developments.

Conclusion: In conclusion, nobiletin has excellent potential as a neuroprotective agent, particularly for diseases such as Alzheimer's. Although its unique structure promotes metabolic stability and membrane permeability, problems with solubility and bioavailability are now limiting practical translation. Its future therapeutic usage depends on addressing these constraints with innovative formulation techniques.

Keywords: Citrus flavonoids, Alzheimer's disease, neuroprotection, nobiletin, bioavailability, and formulation techniques.

INTRODUCTION

Naturally numerous substances are now being considered for clinical medication. Nobiletin (NOB) is known for its non-toxic dietary flavones with a weight of 402.39 g/mol. It is a unique class of flavonoids mostly present in citrus fruits, which is often referred to as Hexa-methoxy flavone. It has the empirical formula $C_{21}H_{22}O_8$ [1]. It is initially isolated in the 1960s, NOB's numerous health advantages have been reported. Citrus peels have been utilized in traditional Chinese medicine for their therapeutic properties, laying the foundation for contemporary pharmacological research that has validated and expanded these uses.

A compound's metabolism and structure determine its bioactivities. Because of its high permeability and lipophilic character, NOB is readily absorbed even in the absence of a glycoside moiety[2], suggesting a particular mechanism. It has been stated that NOB exhibits several therapeutic effects, including anti-inflammatory and anti-cancer[3], antioxidant [4], resistance to insulin anti osteo clastogenesis [5], immune regulation [6], cardioprotective [7], as well as neuroprotection [8]. Furthermore, nobiletin's ability to influence a range of cellular signalling pathways, including those linked to inflammation and lipid metabolism, emphasizes its potential in preventive and therapeutic methods.

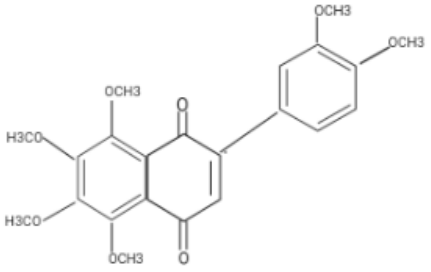

Figure 1: Structure of nobiletin

Chemical properties of nobiletin-

Nobiletin is available in yellow and white in color crystalline powder. Its chemical formula is $C_{21}H_{22}O_8$, and its melting point is around 134°C. It is insoluble in water. Nobiletin is insoluble in ether, benzene, and chloroform but somewhat soluble in petroleum ether. Six methoxy groups with low polarity make up the aromatic hydrocarbon ring in NOB's chemical structure. The covalent bond rotation between the aromatic and methylene rings and alternating methoxy conformations are characteristics of NOB's chiral structural conformation. Because of its methoxylated structure, nobiletin is less prone to hydrolysis than hydroxylated flavonoids, making it more stable in acidic environments sensitive to oxidative stressors and high temperatures.

Sources of nobiletin-

The poly methoxy flavonoid nobiletin is mostly obtained from citrus fruit peels, particularly Citrus reticulata (mandarin orange). NOB is a substance that is extracted and purified from orange peels belonging to the Rutaceous family's genus Citrus. Tangerine, Citrus aurantium, Citrus reticulate, Citrus Sinensis, Citrus depressant, Citrus Unshiu arnica indica, Peels, stems, and leaves of Citrus aurantium and Citrus deliciosa are the main sources of this extract. [9]

Naturally occurring citrus peels, especially those from species like Citrus reticulata (Ponkan mandarin) and Citrus tangerina (Dancy tangerine), are a good source of nobiletin. Because to its extensive array of biological activity and possible therapeutic uses, this molecule has attracted a lot of attention. Currently, chemical synthesis and biological extraction are used to manufacture NOB.[10]

Extraction procedures

The polymethoxy flavonoid nobiletin (NOB), primarily found in citrus peels and possessing a range of pharmacological properties, has been the subject of numerous investigations. There are numerous NOB extraction methods, including:

1. Traditional Extraction Techniques

1.1Extracting Solvents

Solvent extraction remains one of the most often used methods for isolating NOB. Techniques such as ethanol heat reflux and subcritical water extraction have been widely employed. Although these methods often yield adequate levels of NOB, they are widely criticized for their high running costs and limited efficiency.[11]

1.2Refluxing and Maceration

Traditional maceration involves soaking plant materials in solvents for extended periods, whereas refluxing utilizes heat to enhance extraction efficiency. However, these methods are time-consuming and may result in the degradation of sensitive compounds.[12]

2. Sophisticated Extraction Methods

2.1Sonication-

Ultrasound-assisted extraction, or UAE, has gained popularity due to its efficiency and low environmental impact. Studies show that the UAE can produce NOB yields that are comparable to or better than normal procedures while using less solvent and shorter extraction times. Citrus depressa Hayata peels ultrasonically treated with 50% ethanol as a solvent, for instance, significantly enhanced flavonoid yields.[12]

2.2Extraction Assisted by Microwave

Microwave-assisted extraction (MAE), which utilizes microwave energy to heat solvents, is another modern technique that enhances the extraction process. Research indicates that MAE can effectively remove NOB while using less solvent and reducing extraction times.[13]

2.3Extraction of Supercritical Fluid

Due to its ability to selectively dissolve compounds without leaving harmful residues, supercritical fluid extraction (SFE), particularly with supercritical CO_2, has been studied for NOB extraction. It has been shown that increasing the supercritical fluid's ethanol content enhances NOB emission.[14]

3. New Methodologies

3.1Liquid Ionics

Using ionic liquids as solvents is a novel way to improve the extraction efficiency and bioavailability of NOB. These environmentally safe solvents can help make flavonoids more soluble.[13]

3.2 Extraction by Enzyme

Using enzymatic methods, which employ specific enzymes to degrade plant cell walls, NOB extraction has also been investigated. This method can improve yield and purity even if it might call for specific circumstances and longer processing times.[11]

Table 1: Sources, origin, characteristics and uses of Nobiletin

Aspects	Details
Sources	Mostly found in the peels of citrus fruits, such as satsuma mandarin (Citrus unshiu), orange (Citrus sinensis), lemon (Citrus limon), bitter orange (Citrus aurantium), and tangerine (Citrus reticulata). The concentrations in unripe fruits are higher, ranging from 7 to 173 mg/kg of dry weight.
Origin	Nobiletin has the chemical formula C21 because it is a polymethoxylated flavone with six methoxy groups. $H_{22}O_8C_{21}H_{22}O_8$ and 402.4 g/mol as its molecular weight. Its lipophilic properties increase its bioavailability and therapeutic potential by enabling it to pass through cell membranes, including the blood-brain barrier.
Characteristics	-**Look:** Crystalline powder, white or yellowish. **-Solubility:** Absorption is facilitated by lipophilic qualities. **-Stability:** Under storage or gastric circumstances, it can break down into 5-demethylnobiletin.
Uses	**Anticancer Properties:** Regulates cancer-related signalling pathways, causes apoptosis, and inhibits the growth of cancer cells. In **neurodegenerative** illnesses like Alzheimer's, neuroprotection lowers oxidative stress and enhances cognition. In **chronic disorders**, anti-inflammatory effects help to reduce inflammation. **Liver Protection:** Possible therapy for hepatitis and non-alcoholic fatty liver disease.

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Pharmacokinetics of nobiletin-

NOB is primarily broken down in the upper gastrointestinal tract and absorbed in the jejunoileal after consumption. Research on rats has demonstrated the high bioavailability of NOB, with oil suspension exhibiting a 20% bioavailability.[15] Its high bioavailability and favourable membrane permeability are explained by its decreased molecular polarity, which results from the presence of many methoxylates and the absence of glycosides.

Due to its poor solubility, various administration methods have been developed to enhance its use. One of these delivery methods is transdermal ionic liquid administration devices, which have been proven to boost rats' oral NOB use [16] in addition to the self-emulsifying drug delivery technique, which may enhance rats' intestinal absorption [17] . Additionally, the nano-encapsulated amorphous solid dispersion of NOB may have stronger hepatoprotective benefits than crystalline NOB in the ALI rat model due to its higher bioavailability. [18]

Hepatic microsomes and cytochrome 450 are the main liver enzymes that break down NOB. CYP1A1, CYP1A2, and other enzymes catalyse the metabolism of NOB in rats, producing three mono-demethylated metabolites (4-OH-, 7-OH-, and 6-OH-NBL). According to the current study, metabolized demethylated derivatives are primarily responsible for the organism's manifestation of NOB. Rats given NOB orally or by injection showed distinct demethylated products in their plasma, according to in vivo NOB studies. Furthermore, when researchers collected urine samples from rats given NOB orally, they discovered that most of the metabolites in the urine were demethylated derivatives.[19]

Its unique structure—which consists of six methoxy groups—makes it more lipophilic and accessible, which facilitates its passage through biological membranes like the blood-brain barrier. Its broad range of biological activities and possible therapeutic uses are made possible by this characteristic. Following metabolism, NOB is quickly and evenly absorbed by the body, reaching a few organs and tissues. The highest levels of NOB are found in the tissues of the liver and small intestine, followed by the stomach and adipose tissues. In each tissue, the NOB takes around 30 minutes to reach its maximum concentration. [20] NOB is removed through the urine following absorption, metabolism, and transportation. In the colon, any NOB that is not absorbed interacts with intestinal flora before being released as feces. According to studies, fecal NOB and its metabolites contribute 8% of the total dose, while NOB is excreted, and its metabolites provide 7%.

Pharmacological effects of nobiletin

1. Effects of nobiletin on cholinergic deficits

Early on in AD, there has been evidence of a marked decline in olfactory function. [21] The cholinergic system gradually degenerates in tandem with these brain alterations, which cause learning and memory problems. Previously, olfactory bulbectomy (OBX) mice were used to study the neuroprotective effects of nobiletin (50 mg/kg, intraperitoneal [I. p.] or 50-100 mg/kg, oral [p. o.]) after an 11-day treatment schedule [22,23].

This mouse model exhibits memory and learning impairments resulting from cholinergic deficiencies. When OBX-induced associative memory impairment was assessed using the passive avoidance test, nobiletin treatment markedly improved it [22,23]. Similarly, 11 days

after receiving nobiletin (50 mg/kg p. o.) treatment, there was also a reported improvement in short-term memory impairment in the Y-maze test [22,23]. Following 11 days of intraperitoneal nobiletin administration (50 mg/kg), the density of hippocampus AChE-positive fibers was similarly increased by up to 32%. [i. p.], oral [p. o.], or 50–100 mg/kg) treatment, leading to an increase in cholinergic septo hippocampal innervations [22,23]

2. Nobiletin's Impact on Amyloid-beta (Aβ) Pathology

In the pathophysiology of AD, the formation of extracellular Aβ plaques is a crucial stage. According to the amyloid hypothesis, the buildup of Aβ is crucial in relation to AD pathobiology [24]. It has been shown that administering mice with Aβ either acutely or continuously causes synaptic disruption, neuronal death, and cognitive abnormalities that resemble those seen in clinical AD [24,27]. Using the eight-arm radial maze test, one study shown that daily nobiletin (10–50 mg/kg, I. p.) treatment can enhance working and reference memory in rats given chronic Aβ1–40 infusion into the cerebral ventricle via an osmotic pump [25].

Nobiletin may have neuroprotective benefits in transgenic animal models of Alzheimer's disease (AD). However, in APP-Swedish/London (SL) 7-5 Tg mice, which develop Aβ plaques in the entorhinal cortex and hippocampus by 9 months of age, nobiletin treatment (10 mg/kg daily) reduced Aβ pathology and cognitive deficits. The Morris Water Maze was used to test spatial memory deficits, and after four months of therapy, guanidine-soluble Aβ1-40, Aβ1-42, and Aβ plaques significantly decreased. [25]

Another study used a triple transgenic mouse model of AD (3XTg-AD) to examine how nobiletin administration affected amyloid pathology and cognitive impairments. Amyloid plaques, intracellular neurofibrillary tangles with hyperphosphorylated tau protein, and cognitive deficits have all been observed in these rats. Because nobiletin (30 mg/kg) reduced the amount of soluble Aβ1-40 in the brains of 3XTg-AD mice and reduced the generation of free radicals in the hippocampus regions, the mice's short-term memory and recognition memory were superior to those of wild-type mice after three months. [26]

3. Nobiletin's Impact on Ischemic Injury

It has been demonstrated that ischemic damage causes neuropathological alterations resembling AD pathogenesis [27]. For example, it has been demonstrated that arterial carotid blockage causes Aβ oligomer deposition, memory impairments, and synaptic dysfunction in rats [28]. Nobiletin's impact on cerebral Ischemia was studied before [29]. Improvements in the associative memory impairment caused by 5-min BCCAO, or bilateral common carotid artery obstruction were reported utilizing the passive avoidance test after receiving 50 mg/kg nobiletin intraperitoneally for seven days in a row before and after cerebral ischemia. Additionally, the Y-maze test showed enhanced short-term memory. Increases in key synaptic proteins, such as microtubule-associated protein 2 (MAP2), calcium/calmodulin dependent protein kinase II (CaMKII), and GluR1 in the hippocampus CA1 area, have also been linked to improvements in memory [29]. These findings also imply that nobiletin may activate CaMKII signaling to provide neuroprotection.

4. Nobiletin's Impact on Tau Hyperphosphorylation

Senescence-accelerated mice (SAM) have become a popular model for studying the pathobiology of AD due to their early development of memory and learning impairments and several pathological characteristics, including elevated oxidative stress, amyloid neurofibrillary tangles and plaques. In comparison to SAMP8 mice fed a typical chow diet, nobiletin treatment (10–50 mg/kg, i.p.) given daily for one month to SAMP8 mice aged 4-6 months prior demonstrated notable improvements in object recognition memory and attenuated context-dependent fear memory impairment [30]. Nobiletin-treated and non-treated SAMP8 mice did not significantly differ in their anxiety-like behavior, indicating that nobiletin-induced cognitive enhancements might occur independently of the emotional state shift [30].

Furthermore, nobiletin therapy (10–50 mg/kg, I. p.) prevented the rise in tau phosphorylation in the SAMP8 mice's hippocampal region at the Ser202 and Thr231 residues [30]. Retrograde neurodegeneration results from hyperphosphorylation of tau, which also destabilizes microtubules and prevents axonal transit. Consequently, it is probable that nobiletin could be a useful therapy that reduces tau hyperphosphorylation and enhances memory and learning.

5. Nobiletin's Antioxidant Effects

Chronic oxidative stress is one of the primary drivers of ageing and is linked to the pathophysiology of a few neurodegenerative disorders. The antioxidant qualities of nobiletin have been precisely described. [31,32]. Treatment with nobiletin has been demonstrated to stop hydrogen peroxide from killing HT22 cells. [31]

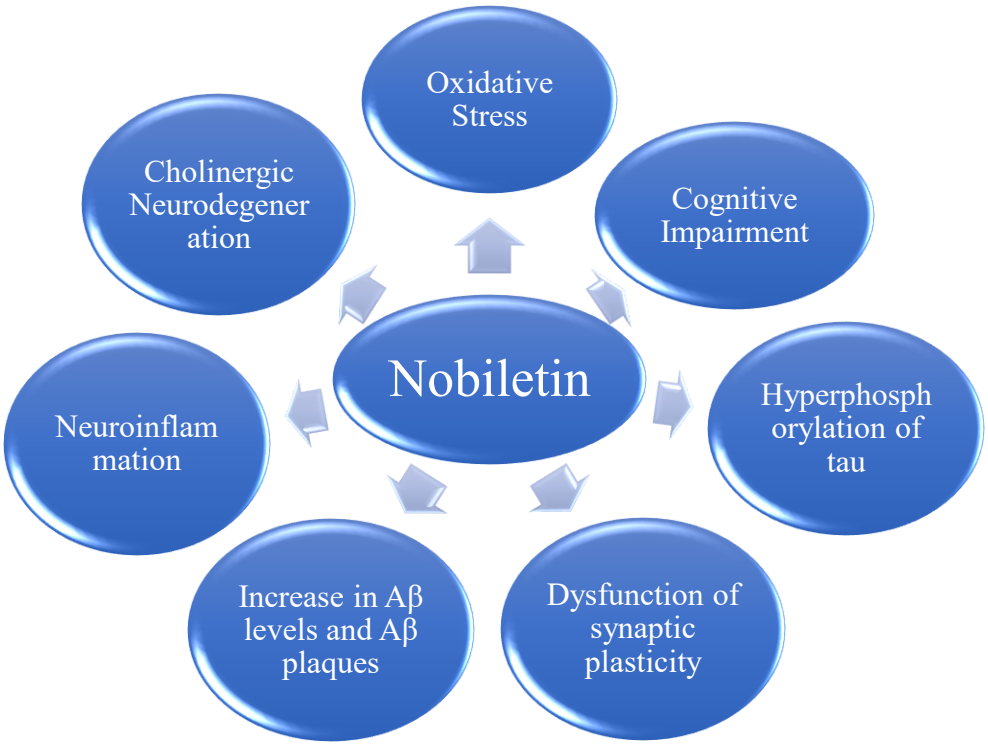

Figure 2: Nobiletin's numerous protective benefits against Alzheimer's disease symptoms

Nobiletin specifically inhibited hydrogen peroxide, which resulted in the expression of phospho-Jun N-terminal kinases (p-JNK) and p-p38 without altering the levels of JNK or p38. Additionally, nobiletin increased Bcl-2 expression in HT22 cells while inhibiting Bax and caspase 3 expression. [31]

Table 2: An overview of research on nobiletin's neuroprotective properties

S. No.	Model	Dose	Effect
1	Mice with olfactory bulbectomy (OBX)	50mg/kg	Improved OBX-induced associative memory impairment as measured using the passive avoidance test
2	Rats continuously injected with Aβ1-40	10 mg/kg	Improved reference and working memory by the application of the eight-arm radial maze test
3	MK-801-exposed mice	10-50mg/kg	Reversed the MK-801-induced context-dependent fear memory loss of 40–70%.
4	Mice that have bilateral common carotid artery blockage	50mg/kg	Enhanced short term memory
5	Mice with accelerated senescence (SAM)	10-50mg/kg	Attenuated context-dependent fear memory impairment and notable gains in object recognition memory

This implies that changes in the expression of mitogen-activated protein kinases and suppression of pro-apoptotic proteins may be the mechanisms by which nobiletin exerts its antioxidant benefits increased amounts of protein carbonyl production and lipid hydroperoxide, and decreased concentrations of antioxidant enzymes like glutathione peroxidase (GPx) and endogenous antioxidants like glutathione (GSH), which have been previously documented in the brains of old SAMP8 mice.

Nobiletin's Toxicity

The poly methoxylated flavone nobiletin has a harmless profile. However, its toxicity in many cell types and tissues has not been thoroughly examined. Despite being derived from natural sources and widely regarded as a safe substance, NOB consumption, whether acute or chronic, may cause physiological alterations in the body. According to a small number of studies in the literature, NOB did not result in any long-term toxicity or a notable decrease in body and liver weight, which is a symptom of vivo toxicity [33,34,35]. Table 3 lists a few research projects including NOB-related formulations, including micelles and nanoparticles, that are connected to toxicity in vitro.

Table 3: In vitro toxicity studies with Nobiletin

Type of toxicity	Subjects/specifies	Dose	Type of formulation	Results/key findings
Cytotoxicity	Human keratinocyte Ha Ca T cells.	100 micrograms	NOB Solution	Growth is significantly inhibited at 100 μM. In HaCaT cells, NOB promoted autophagy rather than apoptosis.
Cytotoxicity	Thyroid cells with T235, T238 and PCCL3 cell lines.	100 micrograms	NOB Solution	NOB reduced cell viability in a way that depends on dosage, much to chemotherapy medications like cisplatin. NOB effectively reduced cell viability at 100 μM, however it was less harmful to healthy cells.
Cytotoxicity	H1299 Cells	Up to 80 micrograms/ml	NOB Loaded Zein nanoparticles.	Exhibited dose-dependent cytotoxicity
Cytotoxicity	RAW264.7 Cells	Up to 37.2 micrograms	NOB Solution and NOB Nano emulsion	Viability was higher than 95% at the maximum concentration.

Table 3 lists a few research projects including NOB-related formulations, including micelles and nanoparticles, that are connected to toxicity in vitro.

Reports on nobiletin formulations

Due to the numerous advantages and safe profile of flavonoids, there has been a recent increase in interest in using them as medicinal agents. However, because of their low permeability and low solubility, these compounds are primarily categorized as BCS class IV [36,37]. Formulation techniques such solubilization, emulsification, amorphous solid dispersion, micelles, and nanoparticles have been thoroughly researched to address these issues of solubility, permeability, and bioavailability. Although it has several uses, its clinical value for therapeutic treatment is limited by its solubility and stability issues. The NOB's biopharmaceutical parameters have a crucial part to turn it into a medicinal product [38,39,40,41]. Due to its poor water solubility in neutral or acidic environments, NOB has a very low bioavailability and is challenging to absorb. At room temperature and body temperature, it also crystallizes easily. Therefore, an adequate formulation must be developed to contain and hold NOB during its transport path to improve its water solubility and bioavailability. [42] The sections that follow go over a few tactics designed specifically to increase NOB solubility, and Table 4 categorizes bioavailability following a review. The many formulation forms developed thus far to improve the solubility and bioavailability of NOB are displayed in Figure 3.

Table 4: Nobiletin Formulations and Nanotechnology-based strategies

S. No.	Type of formulation	Components of delivery system	Key findings
1	Chitosan-Based nano particles	Delivery technique based on polymers made with methanol, acetic acid, and chitosan.	When compared to NOB alone, the nanoparticulate system exhibits an improved anti-tumoral activity. The efficiency of cancer treatment is demonstrated by the repression of cancer cells (IC50=8μg/ml), which also prevents cervical cancer, inhibits invasion and migration in brain tumour cell lines, and has an anti-proliferative effect on breast and ovarian cancer cells.
2	Zein-Based nanoparticles	Zein, tannic acid, and metal solution (FeCl3/AlCl3) are examples of protein-based delivery systems.	The loading capacity and stability during long-term storage are increased by nobiletin encapsulation in ZT-Al NPs and ZT-Fe NPs.
3	Nano emulsions	De-ionized water, medium-chain triacylglycerol, sunflower lecithin, and lipopolysaccharides.	Enhanced anti-inflammatory activity in macrophages produced by LPS, reducing cytokines and mediators of inflammation. RAW 264 activated by LPS. Investigating the anti-inflammatory qualities involved seven cells.

4	Solid dispersions	PEG 6000, PVP K15, methyl hesperidin, α-glucosyl hesperidin, and poloxamer 407 [PEG Solu plus, HPC, HPMC SE-06, HPMC acetate succinate, PVP–vinyl acetate copolymer, and polypropylene glycol (PPG)–PEG block copolymer.	Using highly aqueous-soluble methyl to create a new ASD of poorly aqueous-soluble nobiletin MeHes, or hesperidin. The content of nobiletin in MeHes ASD was noticeably higher than that of other polymer-excipient HME formulations.
5	Emulgels	Hydroxypropyl methylcellulose (HPMC), medium-chain whey protein concentrate, and MCT (triglycerides), calcium chloride	The viscoelasticity of emulgels has changed due to the addition of HPMC, which also prevented nobiletin crystallization and enhanced bio accessibility. The bioaccessibility was evaluated using an in vitro digestion model.
6	Nano micelles	Polymer-based drug delivery system; 2000-block poly (e-caprolactone) 2000-block poly (ethylene glycol).	OVX mice were ovariectomized by RANKL (receptor activator of nuclear factor-κB ligand). The use of cell models to study the impact on osteoclasts and the anti-osteoporosis activity stopped bone loss and enhanced bone density in OVX mice; reduced osteoclast formation of bone marrow-derived macrophages through the RANKL-induced MAPK signal pathway; had no deleterious effects on bone marrow-derived macrophages.

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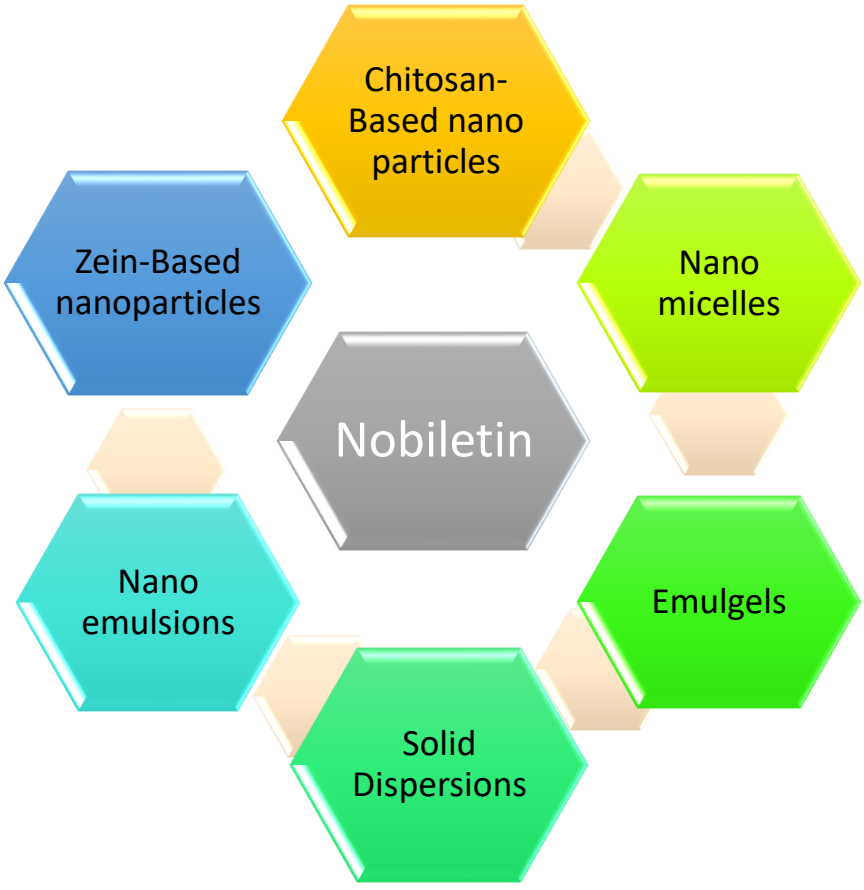

Figure 3: contemporary methods based on formulation development and nanotechnology

The many formulation forms developed thus far to improve the solubility and bioavailability of NOB are displayed in Figure 3.

Table 5: Patents related to nobiletin

S. No.	Country Name	Patent ID	Title of patent
1	China	CN110498784A	Derivatives of nobiletin and their use as P-glycoprotein (P-gp) inhibitors to treat cancers with medication resistance.
2	China	CN105030559A	Drugs and health products that prevent and treat oral cancer are made with nobiletin.
3	China	CN113908148A	Nobiletin's use in the production of anti-cholangiocarcinoma medications.
4	China	CN113018292A	Nobiletin, a BH3 mimetic medication, inhibits small cell lung cancer and works in concert with histone deacetylase inhibitors.
5	Europe	EP2907395A1	Process for producing a chemical from citrus fruits that contains nobiletin and tangeretin.
6	China	CN116768838B	Technique for synthesising a medicinal compound that combines myricetin and nobiletin.

Numerous patents, mostly from China, demonstrate nobiletin's therapeutic potential. These include cholangiocarcinoma, small cell lung cancer, mouth cancer, and drug-resistant malignancies. As demonstrated in a European patent, certain inventions also concentrate on techniques for removing nobiletin from citrus fruits and mixing it with other substances, such as myricetin.

Future prospectives

Bioactive chemicals are abundant in extracts from medicinal and herbal plants that already contain a few bioactive components and have a positive, multi-pharmacological effect. Skin protection is one of the many advantages of orange peel extract. Nobiletin is extracted, purified, and then examined to determine its IC50 and LD50 concentrations as well as to look at its ADME/tox profile in vitro and in vivo. improvement of water solubility through chemical modification, such as glycosylation, or formulation with medicinal excipients. Nobiletin, a significant phytoconstituent, may be investigated as a potential medication after all safety, effectiveness, and stability evidence for human usage have been obtained. Virtual and biological screening are effective methods for determining Nobiletin targets for Nobiletin or its derivative may be promoted as a treatment with the use of the raising modelling/QSAR technique.

Conclusion

Nobiletin, a natural polymethoxyflavone derived from citrus peels, exhibits remarkable therapeutic potential due to its anti-inflammatory, antioxidant, anti-cancer, and neuroprotective properties. Its unique chemical structure ensures stability and high bioavailability, enabling diverse pharmacological activities. Despite its promise in treating conditions such as Alzheimer's disease and ischemic injury, challenges including low water solubility and limited large-scale extraction techniques hinder its clinical application. Addressing these limitations through advanced formulation strategies can unlock its full therapeutic potential.

Abbreviations

1. **NOB:** Nobiletin
2. **AD:** Alzheimer's disease
3. **BCS:** Biopharmaceutical Classification System
4. **OBX:** Olfactory Bulbectomy
5. **i.p.:** Intraperitoneal
6. **p.o.:** Per Os (Oral)
7. **CYP:** Cytochrome P450
8. **MAP$_2$:** Microtubule-Associated Protein 2
9. **CaMKII:** Calcium/Calmodulin-Dependent Protein Kinase II
10. **GSH:** Glutathione
11. **GPx:** Glutathione Peroxidase
12. **SAMP8:** Senescence-Accelerated Mouse Prone 8
13. **HT22:** Hippocampal Neuron Cells 22
14. **3XTg-AD:** Triple Transgenic Mouse Model of Alzheimer's Disease
15. **Aβ:** Amyloid-Beta
16. **ALI:** Acute Liver Injury
17. **BCCAO:** Bilateral Common Carotid Artery Occlusion

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