Nobiletin Prevents Obesity-Related Complications and Neurological Disorders: An Overview of Preclinical and Clinical Studies

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Abstract

Nobiletin (NOB) chemically known as 5, 6, 7, 8, 3, 4-hexamethoxyflavone is a polymethoxylated flavonoid that is predominantly found in the peel of citrus fruits. Animal studies and a limited number of clinical trials suggest that NOB has multifunctional biological activities such as protection against obesity and obesity related cardiometabolic disorders, neuroprotection, antidiabetic, anticancer, anti-allergy, antioxidant, anti-inflammatory, and free radical scavenging abilities. NOB and its metabolites have also displayed antibacterial and antiviral properties and inhibition of hepatic lipogenesis. This review is intended to discuss the pharmacological actions and therapeutic potential of NOB and its metabolites in the prevention of obesity and obesity associated health complications. Evidence obtained from animal studies and a limited number of clinical trials suggest that NOB may be a promising candidate for the prevention of obesity and obesity related disorders as well as non-communicable diseases. Further studies are needed to understand the mechanism of action of NOB at the cellular, genetic, and molecular levels.

Keywords: Nobiletin, obesity, cardiometabolic disorders, inhibition of hepatic lipogenesis, antiatherogenesis.

Introduction : Obesity or corpulence is the most prevalent disorder among all age groups and genders worldwide (1). Body mass index (BMI) is commonly used as a crude measure of obesity. BMI is defined as the person's weight in kilograms divided by the square of height in metres (kg/m^2). As summarized in Table 1, according to the surgical literature, a person of BMI 18.5-25 is considered of normal weight, BMI ≥ 35 or 40 kg/m^2 is severely obese, BMI ≥ 40–44.9 kg/m^2 is morbidly obese, whereas a person with BMI ≥ 45 or 50 kg/m^2 is considered super morbidly obese. Many epidemiological studies and meta-analyses have shown that mortality and morbidity are mostly related to BMI > 35-40 kg/m^2 (2, 3). Generally, a BMI > 32 kg/m^2 is associated with multiple health hazards among females over 16-year old. In the United States, Excessive weight and fatness causes around 111,909 to 365,000 deaths every year in America, and about one million of deaths (7.7%) annually in Europe. It is estimated that obesity lessens life expectancy by about 6-7 years in humans (4). Obesity is the main risk factor behind several non-communicable diseases (NCDs): namely diabetes mellitus, cardiovascular diseases, neurological disorders, nephropathy, and various types of cancers (e.g. lung, breat, prostate, liver, ovarian and colon). Childhood obesity is also increasing day by day, and obese children experience breathing troubles, expanded danger allergies, hypertension, cardiovascular ailment, diabetes mellitus, and learning deficits. It has been observed that a BMI of 30–35 kg/m^2 decreases life expectancy by 2-4 years, while morbid obesity (BMI > 40 kg/m^2) decreases life span by 10 years (5). Besides BMI, there are other methods to measure obesity such as MRI, computed tomography densitometry (CTD), and anthropometry (6).

Table 1. Classification of body mass index (BMI, kg/m^2)

BMI (kg/m^2)	Classification (19)
18.5	Underweight
18.5-25	Normal weight
25.0-30	Overweight
30.0-35	Obese
35.0-40	Severe obesity
40.0-44.9	Morbid Obesity
45-50	Super morbid obesity

While the total amount of white adipose tissue (WAT) in lean adult men or women consists of about 20 %, the quantity of WAT can increase > 40% in obese humans. Excessive fat accumulation results due to an imbalance between energy input and expenditure, consequently leading to obesity, and obesity-related disorders like type2 diabetes, cardiovascular diseases, and hepatic steatosis, which collectively represent one of the leading causes of adulthood morbidity and mortality world-wide. These days, the electronic and print media are making the people aware of the risks associated with weight gain and obesity-related health problems. Many weight reducing dietary formulations are being promoted in both the developing and developed countries. The intake of weight reducing medications has also increased in the fastpacing world and the overuse of weight loss drugs can create negative impact on the user's health. Users of the ant-obesity drugs and sudden weight loss may experience iatrogenic complications such as cardiac disorders, hypertension, and low energy levels (7). Quite often, after leaving the weight loss medicines, the users regain the weight. Another procedure for weight loss is gastric bypass surgery in which a patient has to be on a liquid diet for about one month and reduce about 25% of the total weight along with the remission rate for the type 2 Diabetes (T2DM) (8). The gastric bypass surgery has some limitations, because people having a BMI ≥35 kg/m^2 generally go through this surgical procedure (9), and others with lower BMI are excluded.

In view of the above observations, there is a need for cost-effective, safe and effective strategies for the prevention of obesity and obesity-related complication like T2DM, metabolic disorders and cardiovascular diseases (10). Several studies have shown inverse relationship between the obesity and the intake of dietary flavonoid. The flavonoids are a diverse group of phytonutrients present in all citrus fruits and many yellow color vegetables. The flavonoids are the largest group of phytonutrients and more than 6,000 types have been identified in natural products (11). Active research is going on the citrus-derived flavonoids like nobiletin and naringenin for the prevention of obesity, metabolic disorders, and cardiovascular diseases (12). Nobiletin was discovered in 1930's by a Chinese scientist Kwong-Fong Tseng, who isolated nobiletin from Chen-pi, a Chinese drug made from the citrus fruit peel of mandarin orange by using cold methanol extraction technique. Nobiletin and other flavonoids have antioxidant and anti-inflammatory properties, promote insulin sensitivity, and inhibit apo-B100 secretion from cultured hepatocytes (13, 14). Studies in high-fat-fed mice revealed that supplementation with nobiletin and naringenin reduced weight gain and adiposity, prevented hepatic steatosis, and lowered the atherosclerosis progression (15). In another study, nobiletin improved hyperglycemia and insulin resistance in obese diabetic mice and decreased the secretion of an insulin resistance factor resistin in 3T3-L1 adipocytes (16). In a mouse model of metabolic syndrome, nobiletin markedly attenuated metabolic dysregulation and slowed the development of atherosclerosis (17,

18). Citrus peel extracts rich in polymethoxyflavones (PMFs) have demonstrated a promising therapeutic effect for metabolic disorders (19).

Bioavailability, pharmacokinetics, and metabolic disposition of Nobiletin: Many phytochemicals have incontestable promising chemopreventive effects in cell line studies, however their bioefficacy in vivo is commonly restricted because of the low oral bioavailability. The limiting factors for the oral bioavailability of phytochemicals square measure classified into 3 major categories: bioaccessibility, absorption, and biotransformation (20).

Bioaccessibility is the requirement for bioavailability and is outlined because the probably absorbable quantity of phytochemical within the lumen once the channel digestion (21).

The absorption refers to the fraction of phytochemical transported across the enteral animal tissue. It is associated with the chemical science properties of the phytochemical molecules, together with their lipophilicity, atomic number bonding capability, molecular size, etc. (22).

The biotransformation of phytochemicals in vivo yields in depth metabolites by gut microbiota and also the host. The generation of metabolites plays a crucial role on the bioavailability and bioactivity of phytochemicals in vivo.

Nobiletin, one among the foremost current citrus polymethoxyflavones (PMFs), has received abundant attention for its promising biological activities, like anti-obesity, anti-inflammation, and anti-cardiovascular unwellness, etc. (23). Nobiletin has six methoxy groups on the five,6,7,8,3',4'-positions of the flavone skeleton. The multiple methoxy teams alter nobiletin smart membrane permeability however poor bioaccessibility thanks to the restricted water solubility. Totally different encapsulation methods, victimisation emulsion systems, hydrogels, nanoparticles, and amorphous solid dispersions, are developed to reinforce the bioaccessibility of PMFs. In vitro models square measure usually used because the screening methodology for various delivery systems, despite the fact that these models square measure criticized for his or her simple conditions mimicking the duct surroundings (24).

There are studies which shows that nobiletin can be orally administered along with intravenously. For the oral administration, mice got nobiletin delivered by oil suspension (2% w/v) or emulsion (1%, w/v) at the indefinite quantity of a hundred mg/kg. For the shot, nobiletin was dissolved in five% DMSO and two hundredth Tween eighty and given to rats via tail vein injection at the dose of five mg/kg. Blood samples were collected in heparin-coated tubes at the 0.5, 1, 2, 4, 6, 10 and 24 h when the administration of nobiletin. The plasma samples were obtained by centrifuging blood samples at 5000 revolutions per minute for fifteen min. To assess the concentration of nobiletin within the plasma, two hundred µL plasma was treated with sulfatase and β-glucuronidase and incubated at 37°C for forty-five min. The treatment of enzymes was to unharness the conjugated demethylated metabolites, that permits us calculable the overall

demethylation biotransformation of nobiletin within the blood. Then centrifugation at 10000rpm for 3 minutes and then the supernatant was combined and evaporated by using flowing nitrogen. 200µL of 80% methanol with a concentration of 0.2% acetate was used to again dissolve the pallet and refilterd 0.22µm of the nylon filter (25).

Absolute bioavailability of Nobiletin

$F\ (\%) = (AUCpo * Doseiv)\ (AUCiv * Dosepo) * 100$

Where AUC= area under the curve, which represented for the integral of nobiletin concentration in the plasma against the definite time. The data showed that the most important metabolites square measure demethylated nobiletin, like mono- and di-demethylation merchandise, and sulfation and glucuronation of metabolites additionally detected in nobiletin biotransformation. The demethylation happens mainly at the B-ring of C6–C3–C6 flavone skeleton with the formation of thirty -, 40 -, and 30 , 40 -di-desmethylated PMFs, with the exception of some P450 enzymes that born-again nobiletin to its 6-, 7- and 40 -desmethylated counterparts. Hence, we tend to over that nobiletin metabolic pathway primarily undergoes B-ring demethylation. more investigations of nobiletin biotransformation, notably in several tissues in varied animal species and human subjects square measure necessary to own a higher understanding of PMF metabolic pathways since there square measure more and a lot of potential applications of nobiletin and different citrus PMFs in hindrance and intervention of human diseases (26).

Harmful bioactive chemicals secreted by the white adipocytes

While the total amount of white adipose tissue (WAT) in lean adult men or women consists of about 20 %, the quantity of WAT can increase > 40% in obese humans. Even in a lean person, WAT consist of 15-20% of total body weight. WAT is further divided into stromal-vascular cells such as fibroblasts and endothelial, immune and stem cells. Accordingly, two major disciplines of adipobiology have emerged in the biomedical sciences, viz., adipoendocrinology involves studying the endocrine activity of adipose tissue, whereas adipoparacrinology involves studying the paracrine activity of adipose tissue. Both disciplines deal with the pathophysiology of obesity-related diseases (27). WATs secrete a wide range of bioactive substances, such as adipokines, cytokines, chemokines, neurotrophic factors, neuropeptides, steroid hormones, and hypothalamic hormone releasing factors. They also secrete all components of renin-angiotensin system, free fatty acids, fatty acid binding protein-4 (FABP-4), prostaglandins, endocannabinoinds, nitric oxide (NO), hydrogen sulphide (H_2S), and homocysteine. Adipokines regulate appetite, insulin sensitivity, angiogenesis, blood pressure, and immune response. Obesity-induced up-regulation of inflammatory cytokines and interleukins (IL6, IL8) are linked with pathological conditions

such as atherosclerosis, hypertension, hyperlipidemia, heart attack, stroke, and various types of cancers. Since about 70 % of adipose tissue mass is composed of lipids, the adipose tissue represents a major reservoir for many different lipophilic endogenous molecules, environmental toxicants and xenobiotics, which may modulate the activity of key transcription factors in genes engaged in the control of differentiation and secretion from WAT, and the pathogenesis of obesity-related cardiometabolic syndrome and associated disorders (28, 29, 30).

Most of these lipophilic xenobiotics are resistant to biological and chemical degradation; they were dubbed persistent organic pollutants (POPs). There is now increasing evidence that exposure to POPs including chlorinated pesticides and polychlorinated biphenyls may contribute to the pathogenesis of low-grade inflammatory diseases such as atherosclerosis, obesity, type 2 diabetes, and metabolic syndrome. Likewise, xenobiotic-metabolizing cytochromes-P450 (CYP_{450}) are expressed in adipose tissue and are inducible through mechanisms like those in the liver. Because of the secretion of these harmful endogenous metabolites by the WAT, the term has been coined as adipotoxicology. There are other pathways by which endocrine, paracrine, autocrine, and intracrine, along with exosomes and ectosomes get secreted (31).

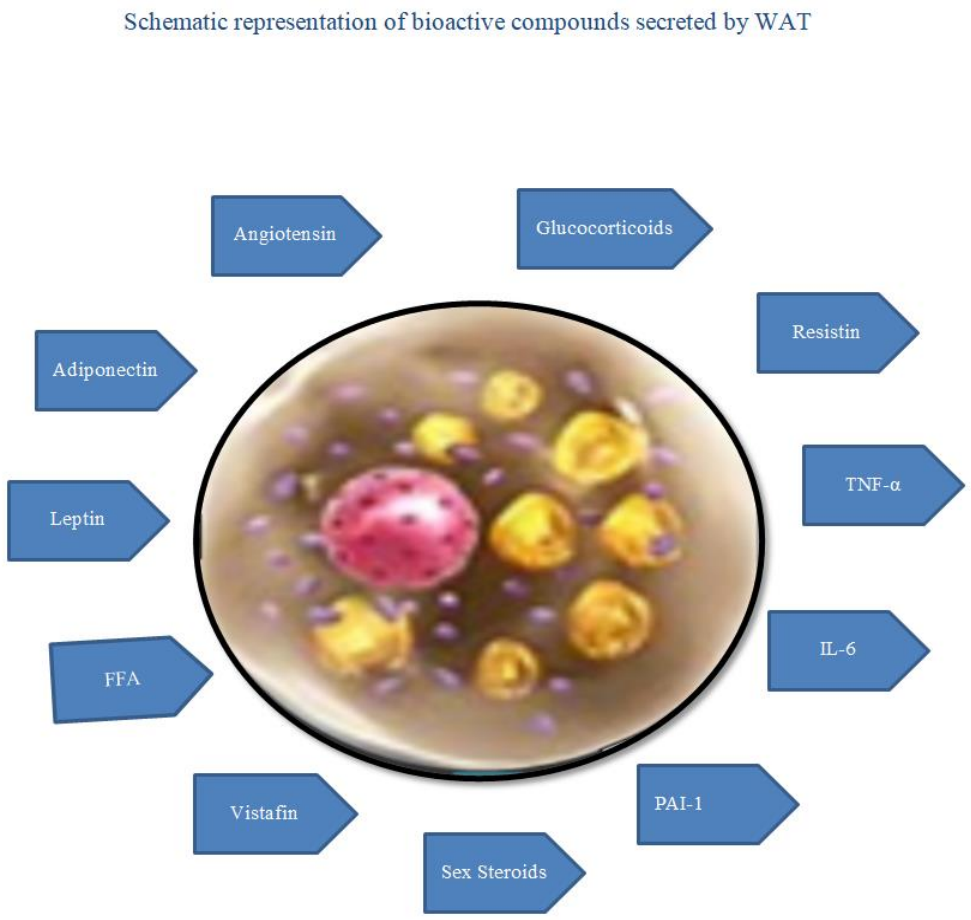


Figure1. Schematic representation of multiple bioactive compounds secreted by WAT.

Table 2: Various adipokines secreted from WAT and their biological actions (32).

Adipokines	Biological actions
IL-6	Inflammation, insulin resistance
TGFβ	Vascular disorder
TNFα	Insulin resistance, lipolysis, adipogenesis, cell survival, inflammation
FGF21	Browning of fatty tissue, thermogenesis
PAI-1	Vascular diseases, fibrinolysis, vessel wall remodeling
Adiponectin	Cell growth, cardiovascular protection, energy expenditure, Inflammation, insulin sensitivity, suppression of What??
Leptin	Angiogenesis, β-cell function, regulation of food intake, energy expenditure, immune response, reproduction, hematopoiesis, osteogenesis, gastrointestinal functions
Chemerin, Apelin, MCP1	Inflammation
Resistin	Insulin resistance, inflammation

Source: Adapted from Luo & Liu, 2016.

Main flavonoids found in citrus fruits

Flavonoids are polyphenols and they are ubiquitous in nature. Out of almost 6000 flavonoids identified citrus peels are the rich sources of flavonoids, even more than that of their edible parts (33). Depending on the chemical structure these flavonoids can be divided into six parts: flavanones, flavonols, isoflavones, anthocyanidins, flavones and flavanols (34). Other than that Neoeriocitrin, naringin and neohesperidin are the main flavanones found in the peels of bergamote, lemon and orange with values 400–1000 mg/100 g peel for bergamote, 400–600 mg/100 g peel for lemon peel and 380–1100 mg/ 100 g peel for the peels of sour orange (35, 36).

On the other hand, hesperidin and narirutin are the most abundant flavonoids in sweet orange (270–350 mg/100 g dry peel) (37), whereas naringin is the most abundant in grapefruit and bitter orange peels (1400 mg/100 g peel) (38). Fig. 1 Chemical structure of Nobiletin (39)**;** Fig. 2 Major flavonoids found in citrus species (40).

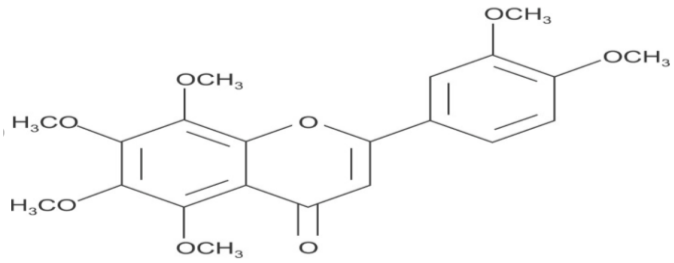
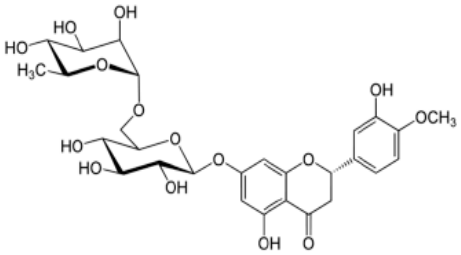
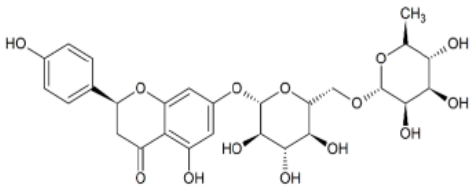


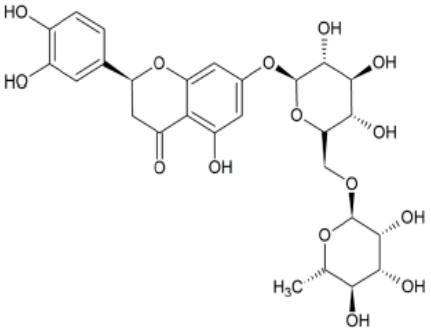
Figure 2: Chemical structure of nobiletin.



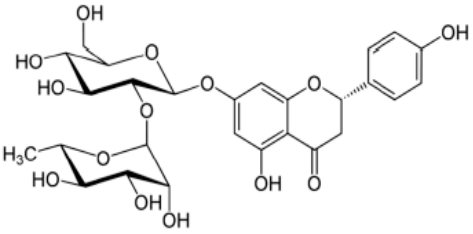
Hesperidin



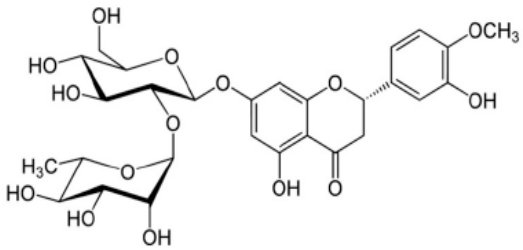
Narirutin



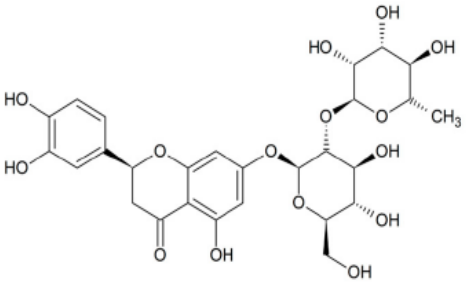
Eriocitrin



Naringin



Neohesperidin



Neoeriocitrin

Figure 3: Chemical structures of major flavonoids found in citrus fruits

Studies done with citrus peel extracts in obese animal models

Flavonoid (µM)	Duration of study	Animal or cell type	Study outcome	References
Nobiletin (0.1% and 0.3% of diet)	4 weeks	Male *Ldlr−/−* mice on a high-fat diet	Decreased VLDL-TG secretion, decreased plasma and hepatic lipids; decreased lipid synthesis	(44)
Nobiletin (0.3% of diet)	4 weeks	High-fat-fed *Ldlr−/−* mice	Reduced glucose and insulin; improved glucose tolerance	(44)
Nobiletin (0.3% of diet)	8 weeks	*Ldlr−/−* mice fed a high-fat Diet	Reduced body weight; prevented adipocyte Hypertrophy	(44)
Nobiletin (50 mg/kg)	-	Bilateral common carotid artery occlusion mice	Enhanced short-term memory	(45)
Nobiletin (50mg/kg)	1 Year	Rats exposed to unilateral injections of MPTP	Ca (2+)/calmodulin-dependent protein kinase II (CaMKII) autophosphorylation and phosphorylation at Thr-34 of dopamine- and cAMP-regulated phosphoprotein-32 (DARPP-32) in the striatum and hippocampal CA1 region were restored to control levels	(46)
Nobiletin (30-100 µM)	-	HT22 cells exposed to hydrogen peroxide	Suppressed caspase 3 and Bax expression, but induced Bcl-2 expression	(47)
Nobiletin (10, 20, and 50 µM)	24 to 48 hours	Human Aortic valves	By activation of ABCG2 and AKR1B1, NOB suppresses tumor necrosis factor (TNF)-mediated calcification of the human aortic valve	(48)

Nobiletin (20, 40, and 80 µM & 20 mg/kg)	8 weeks	Primary human chondrocytes	Alleviation of osteoarthritis by downregulation of PI3K/Akt/NF-kB pathway and reducing Inflammatory factors.	(49)
5, 10, 20, and 30 µM	24 hours	Human mesangial cells	By inhibition of STAT3, NOB downregulates the expression of NF-kB to decrease the levels of TNF-α, IL-6, and IL-1β.	(50)

The constriction of adiposity and adipocyte provocative reactions by citrus flavonoids are seen in numerous creatures contemplates. Although evidences recommend that these impacts are optional to improved hepatic and plasma lipid transport, an immediate effect of citrus flavonoids on adipocyte science has been recorded. Ample numbers of in vitro studies are available to show the effects of citrus peel flavonoids on obesity and associated disorders. One of them is the role of citrus peel compounds in adipocytes or adipocyte apoptosis, it has been seen that on addition of polymethoxyflavones of citrus peel they cause a dramatic enhancement in the intracellular calcium, which is responsible for the increase in calpain alongwith caspase-12 (proteins which are associated with the apoptosis). As the number of adipocytes will decrease due to programmed cell death it could help in weight loss and maintenance of weight (41).

One study done with citrus bioactive compound nobiletin in 3T3-L1 fat cells, resulted in reduced transcription factors which is directly linked with the differentiation of the pre- adipocytes in the mature adipocytes. This resulted in the lowering of lipid deposition in the cultured cells on the addition of flavonoid (42).

Table 3. Preclinical studies done with nobiletin and their outcomes

In an another study rats were fed high fat diet (about 42% of the total calories) along with naringenin or nobiletin (3% and 0.3% respectively) and found a dramatic decrease in the hepatic overproduction of VLDL (very low density lipoproteins), improvement in lipid levels, and also prevented from the hepatic steatosis (43). The decreased hepatic lipid accumulation was related with a decrease in articulation of qualities encoding proteins for a new lipogenesis and an expansion in those engaged with β-oxidation, coming about in diminished hepatic unsaturated fat union and diminished unsaturated fat oxidation. Also, naringenin lessened dyslipidemia, hepatic lipid aggregation, and hepatic irritation in Ldlr−/− mice took

care of either a cholesterol-rich, high-fat eating routine or a cholesterol-rich, low-fat, high-sucrose diet (51). In the liver of male ICR mice, naringenin (1%), yet not hesperetin (1%), expanded the quality and protein articulation of chemicals engaged with peroxisomal β-oxidation (52). Correspondingly, a low-fat eating regimen enhanced with naringenin (0.012%) took care of to rodents for about a month and a half diminished plasma lipids and lessened hepatic steatosis through upregulation of the outflow of qualities managing hepatic unsaturated fat oxidation.

In a report, nobiletin decreases memory decline in the AD model rodents by reestablishing βamyloid-weakened cAMP reaction component restricting protein phosphorylation (53). For a situation study, nobiletin could forestall the movement of psychological impedance in donepezil pre managed AD patients utilizing the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-J cog) (54). In that review, an every day portion of 30 g of nobiletin was blended in with 500 mL of water and decocted until the volume was decreased to 300 mL. At that point, 100 mL of aliquot was given to patients three times each day for 1 year. In addition, different investigations have indicated that nobiletin reestablished psychological shortfalls in creature models of AD (55, 56) and PD (46).

Nobiletin as an antioxidant

Chronic oxidative stress assumes a key job in the maturing procedure and is related with the pathobiology of a few neurodegenerative ailments (47, 39). Treatment with nobiletin has been appeared to hinder cell death because of hydrogen peroxide in HT22 cells (47). Specifically, nobiletin suppressed hydrogen peroxide, which induced the expression of phospho-Jun N-terminal kinases (p-JNK) and p-p38 without changing the degrees of JNK or p38. Nobiletin additionally suppresssed caspase 3 and Bax articulation, yet instigated Bcl-2 articulation in HT22 cells. This recommends the cell reinforcement impacts of nobiletin might be intervened through modifications in the outflow of mitogen-enacted protein kinases and restraint of star apoptotic protein. Raised degrees of lipid hydroperoxide and protein carbonyl development, and diminished degrees of endogenous cancer prevention agents, for example, glutathione (GSH), and cell reinforcement chemicals like a glutathione peroxidase (GPx), which have been recently revealed in the mind of matured SAMP8 mice. Nobiletin has been demonstrated attenuate the decrease in the GSH/GSSG proportion in SAMP8 mice, and essentially increment the movement of GPx in SAMP8 mice. These progressions happened corresponding to a decrease in the degrees of protein carbonyl; a proportion of protein oxidation. The neuroprotective impacts of nobiletin might be intervened, at any rate to some extent through guideline of endogenous cancer prevention agent resistance systems in the brain.

Adipose tissue reduction and weight loss effects of nobiletin

There are various studies in which citrus flavonoids are being used for evaluating the effects of corpulence. Out of them one mechanism is the role of the citrus compounds in adipocyte apoptosis, it was seen that on addition of the polymethoxyflavones of citrus fruits (100µM) it cause an enhanced level of calcium in the cells, which is responsible for the increase in calpain and caspase-12, the proteins associated with apoptosis (41). Due to the decreased number of adipose cells because of apoptosis it could assist the weight loss.

Anti-inflammation and anti-atherogenic effects of nobiletin

No human examinations till date have tentatively inspected the effect of citrus flavonoids on cardiovascular diseases results. Notwithstanding research on the impacts of citrus compounds (flavonoids) on plasma lipids, glucose digestion, and adiposity (evaluated in past segments), clinical investigations analyzing the impacts of citrus bioactive compounds on other CVD biomarkers have been accounted for. Everyday utilization of flavanones rich grapefruit for about four to five weeks has been appeared to diminish diastolic pulse (57). In the healthy men, utilization of squeezed orange (500 ml/day) or hesperidin (292 mg/day) for four weeks altogether improved endothelium-subordinate vasodilation six hours after ingestion (58). Another examination, where unadulterated hesperidin was controlled (500 mg/day for three weeks), came about in altogether expanded stream interceded widening in rewarded subjects contrasted and control subject (59).

Anticancer activity of nobiletin

Research has proved that on administration of a blend of nobiletin and its significant metabolites for 19 weeks to a mice with colitis-related colon carcinogenesis brought about a lessening in cell cycle movement in the colon tissue, which was at any rate halfway identified with down-guideline of inducible nitric oxide synthase (60).

The novel coronavirus disease is being caused by acute respiratory syndrome. The noble coronavirus disease is caused by severe acute respiratory syndrome it has created so much of the problem for the whole world and it is affecting almost 180 countries (61). As a result there has been so much of the economic distress all over the world and the significant loss of the life. People of all the ages can be affected by coronavirus and the risk becomes severe if person is 60 + years and if he or she has any of the pre-existing disease like cardiovascular disease, cancer, diabetes, COPD. Nutrition plays an important role in the prevention and treatment of covid-19. Malnourishment can weaken the immune system in the elderly so it makes them susceptible to the infections that's why a healthy and balanced diet is necessary which is full of macro and micronutrients, prebiotics, probiotics. There are foods in the Mediterranean diet which have

beneficial effects against and also prevent from infections such as covid-19, as they affect the immune health (62). Fruits and vegetable intake should be high it is investigated that fruits and vegetables have potential benefits in association with respiratory and inflammatory conditions due to their high nutrient profile, including vitamins, minerals, antioxidants and phytochemicals (63). Phytochemicals can be anti-inflammatory with other beneficial effects. Vitamin C plays important role when suffering with any of the infections like cold and flu [58]. It has been observed that nutrients with antithrombotic antioxidant and anti-inflammatory properties may attenuate the inflammatory and vascular manifestations which are associated with covid-19. Even by following a healthy diet and avoiding unhealthy food products it also significantly protects from infections (64).

A recent study by Cheng et al., 2020 on citrus flavonoids has shown that naringin could supress the expression of proinflammatory cytokines which is being induced by the LPS in vitro. It was further shown that naringin could limit cytokine through hindering HMGB1 articulation in a myocardial ischemic/reperfusion injury model. The outcomes recommended that naringin could have a potential in forestalling cytokine tempests of COVID-19. The sub-atomic docking result anticipated that naringin and hesperetin had more grounded official liking the ACE2. They proposed that these two phytochemicals, e.g., hesperetin and naringin are most potential mixes focusing on ACE2 receptor, which could forestall coronavirus contamination (65). Chinese customary medication is playing a significant job in the treatment of COVID-19. According to these researchers' people should give more consideration to characteristic mixes structure citrus and other home grown medication to battle coronavirus later on.

A few Finland based researchers reported about the different dose interventions of vitamin C, intravenously (e.g., 200 mg/kg body weight/day, divided into 4 doses) reduce the period of critical care unit stay upto 7.8% (66), alongwith reduced rate of mortality (67). They studied on seriously ill patients and found to be reduced level of oxidative stress, which is induced by the lung injury in ventilator patients (68, 69). Even orally consumed vitamin C can attenuate the risk of viral infections or it could improve the condition (70).

Development of vaccines for the treatment of COVID-19 may take more time, but meanwhile vitamin C and other foods rich in antioxidants can mitigate the symptoms of ARDS (Acute respiratory distress syndrome) associated with COVID-19.

Nobiletin in the management of Alzheimer's disease and Parkinson's disease

The most common age-related neurodegenerative diseases are Alzheimer's disease (AD) and Parkinson's disease (PD) characterized by memory loss and poor quality of life of AD and PD patients. Currently available therapies cannot alter the progression of these diseases. Nobiletin has shown anti-dementia and

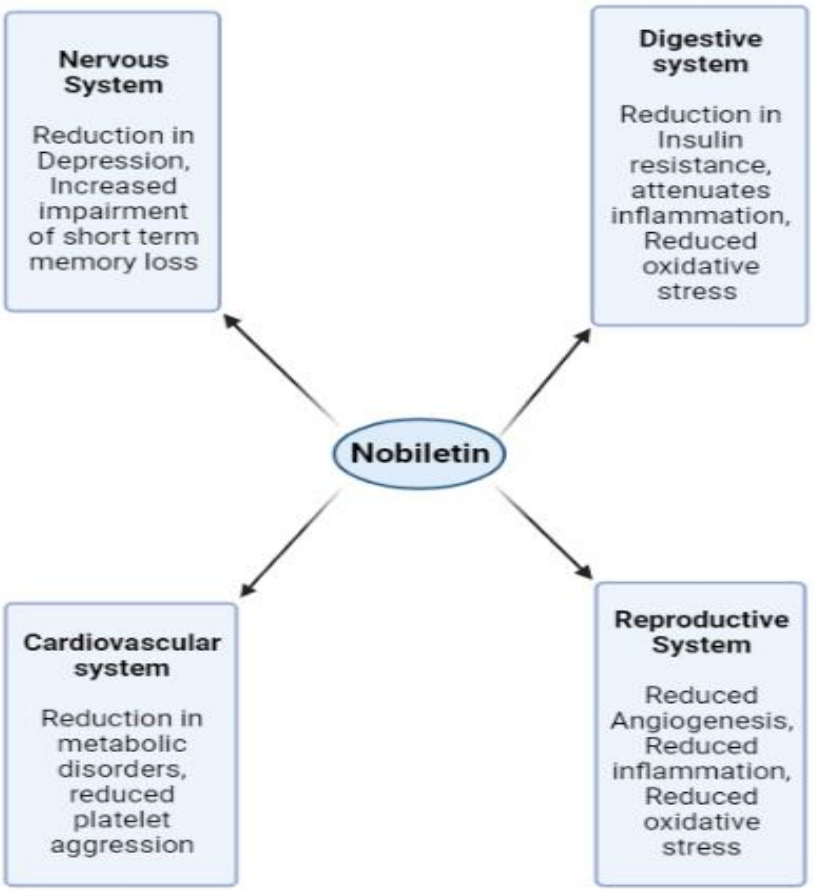
neuroprotective activity in AD and PD animal models (71). However, further evidence from clinical trials is needed to establish the therapeutic potential of nobiletin and its safety and efficacy in AD and PD patients.

In 2015, the total number of dementia and cognition deficit patients worldwide was about 46.8 million, and they are estimated to increase to 131.5 million by the year 2050 (72). Among the neurological abnormalities, Alzheimer's disease is the most serious chronic neurodegenerative disorder characterized by memory loss and poor quality of life and total dependency of patients on the health care providers.

Yasuda et al. (73) observed that administration of nobiletin (10-25mg/kg) for a period of three days before surgery and just after the surgery reduced brain edema in rats. In addition, the infarct volume was also degreased in nobiletin treated rats. RT-PCR, western blotting, and immunohistochemistry essays revealed that after nobiletin administration, the activities of Akt and Bcl-2 were enhanced. These findings suggested that nobiletin protects brain against ischemic damage due to the activation of Akt/CREB pathways and down-regulation of NF-Kb expression along with the amelioration of blood–brain barrier permeability.

Coordinate Regulation of Cholesterol and Bile Acid Metabolism by the Clock Modifier Nobiletin: A current study by Nohara et al., (74) illustrates the key restrictive role of time unit clocks in cholesterol/bile acid homeostasis. This study showed that Nobiletin (NOB), a natural compound that activates RORs and so time unit rhythms, considerably improved body fluid LDL/HDL magnitude relation, and normalized serum and faecal steroid levels in aged mice challenged with high-fat diet feeding. In accordance, NOB was found to boost the expression of steroid synthesis genes within the liver, and shield overall liver health from metabolic challenge. Microbial 16S sequencing more unconcealed that nobiletin alters microbial taxa known to modulate steroid production. Together, this work provides proof that a medical specialty agent targeting the time unit clock powerfully improves cholesterin and steroid homeostasis in a very general manner.

Figure 3: Summary of pharmacological effects of nobiletin



Discussion and conclusions

Nobiletin is one amongst the foremost easy flavonoids in citrus genus and present in citrus peels with giant proportion content. There area unit tremendous scientific findings and evidences according that supported its biological activities as well as inhibition of inflammation, anti-cancer, anti-obesity, anti-diabetic and interference of metabolic syndrome etc. Nobiletin's biotransformation plays an important role within the biological effects and has been studied extensively recently. Therefore, nobiletin and its metabolites have nice potential to become efficacious medical specialty for human diseases. The constriction of adiposity and adipocyte provocative reactions by citrus flavonoids are seen in numerous creatures contemplates. Citrus flavonoids have ground-breaking and various organic properties. The physiologically applicable impacts of citrus nourishments are in all likelihood because of the flavonoid compounds. Advancement of bioavailability and assurance of powerful portions of segregated individual citrus flavonoids (or blends) are required for these mixes to accomplish their full restorative potential. Animal examinations demonstrate that citrus flavonoids decline plasma lipids, decrease hepatic lipid content, and stifle hepatic irritation

principally through an immediate actuation of fatty acid oxidation and a decline in hepatic unsaturated fat combination.

Animal model studies show that citrus flavonoids improve glucose resilience what's more, upgrade insulin affectability, impacts basically identified with improved hepatic and plasma lipids, albeit an immediate impact on catalysts and transporters associated with glucose digestion in liver and muscle has been accounted for. Animal models show antiobesity, anti-diabetic, anti-inflammatory, anti-oxidative effects on consumption of nobiletin.

In summary, our review highlights the therapeutic potential of nobiletin in the prevention of obesity and obesity-related disorders. Intake of diets containing nobiletin may not only prevent obesity, but also obesity-related complications such as type 2 diabetes, insulin resistance, metabolic syndrome, and nephropathy, improve lipid profile, and reduce hepatic steatosis as well as atherosclerosis, cardiovascular disorders and neurological abnormalities. Further well- designed, placebo-controlled, randomised, multi-centre trials are needed to evaluate the long-term safety, efficacy, and appropriate dose regimens of nobiletin in humans.

Conflict of Interest: The authors declare no conflict of interest.

ABBREVIATIONS USED-

PMF-polymethoxyflavone

BMI- Body mass index

WAT-White adipose tissue

NCDs-Non communicable diseases

PMFs-Polymethoxy flavones

DMSO- dimethyl sulfoxide

AUC- area under the curve

RORs- Retinoic acid-related orphan receptor

NOB-Nobiletin

LDL- Low density lipoprotein

HDL-High density lipoprotein

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