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Review Article

A Spotlight on Chemical Constituents and Pharmacological Activities of *Nigella glandulifera* Freyn et Sint Seeds

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Plants belonging to the Ranunculaceae family, and particularly their seeds, have been a hot research topic in numerous pharmacognosy laboratories. *Nigella glandulifera* Freyn et Sint (NG) is one of the promising, but relatively insufficiently studied, plants from this family. In this review, we summarize the recently isolated chemical constituents from the seeds of this plant including alkaloids, flavonol glycosides, isobenzofuranone derivatives, saponins, terpenes, terpenoids, and fatty acids. We put also a spotlight on the recently studied therapeutic potentials of such amazing herb seeds as antidiabetes, melanogenesis inhibition, anticancer, anti-inflammatory, antithrombosis, and antiplatelet aggregation effects. Herein, we illustrate certain properties and potentials via selected examples, and thus we suggest more studies to confirm the therapeutic hypotheses, find out new compounds, and eventually to discover novel properties.

1. Introduction

Medicinal plants from the buttercup family (Ranunculaceae) have been applied extensively for many years to treat various diseases, particularly the seeds. The Chinese plant NG is an annual erect herbaceous plant from this family [1]. It has been reported that NG seeds have diuretic, spasmolytic, analgesic, galactagogue, and bronchodilator effects. Because of their medicinal effects as a natural product, they have been used for a long time to treat urinary calculus, oedema, and bronchial asthma [2].

For the last three decades, three alkaloids with indazole ring system, namely, nigeglanine, nigellicine, and nigellidine, have been isolated from two plants of this family, that is, *Nigella sativa* (NS) and NG [3]. Indazoles are rare in nature, and these are the only three natural products based on indazole ring being isolated [4]. The indazole ring system attracts great interest as partial structure of numerous biologically active compounds [4], hence, the importance of this family in pharmacological research.

Nigella genus consists of about 20 species, including NG, NS, and *Nigella damascena*, which are used in traditional medicine [5]. In southwest and western part of China (Xinjiang autonomous region, Yunnan and Tibet), NG is distributed widely and its seeds have been used since antiquity. NG seeds are mentioned in the Pharmacopoeia of China since 1997 [1, 2, 6, 7]. This review aims to put a spotlight on this plant relatively lacking in studies and research compared to other herbs of the same genus, such as NS. We aim also to provide a useful summary of compounds isolated recently from NG seeds and their potential therapeutical properties newly discovered.

NG seeds are rich in various chemical constituents, such as alkaloids [1], flavonol glycosides [8], isobenzofuranone derivatives [9], saponins [9, 10] terpenes, terpenoids [11] and fatty acids [6]. This plant's seeds are used not only as a spice but also as a treatment of some diseases, such as bronchial asthma, in southwest and western part of China [10]. Recently, more and more scientists are trying to test chemical constituents and therapeutical capacities of this herb. This plant seeds contain p-cymene and thujene, which may interfere with dephosphorylation of the insulin receptor and leptin signaling [12], and also oleic acid methyl ester and dioctyl phthalate (DOP) that inhibit the melanogenesis [13, 14]. They contain also kalopanaxsaponins A and I, which may be potential therapeutic agents to treat the parental and drug resistant hepatoma [2]. In addition, NG seeds total saponins have been reported as having an anti-inflammatory effect

[15]. Some animal experiments also suggest that the linoleic acid in NG seeds oil has an antithrombosis, antiplatelet aggregation and an ability to reduce serum triglycerides [16]. However, it is still unclear whether the therapeutical activities found in NG seeds can be used as a treatment for humankind diseases, and whether they would present any side effects.

2. Chemical Constituents Isolated from NG Seeds

2.1. Alkaloids. Nigeglanine and its artificial derivative (named Nigeglapine [17]) have been isolated from the seeds of this plant, together with fuzitine (a known aporphine alkaloid) [1]. Nigeglanine is based on indazole ring system, and this structure is seldom found in natural compounds [4]. Moreover, the indazole ring system is very interesting as partial structure of many bioactive compounds [18]. For instance, a novel class of human bradykinin B1 receptor antagonists consist of indazole derivatives [18]. A structure-activity relationship examination of the indazole moiety in some compounds was performed en route as participating for an optimal bradykinin B1antagonist [18]. The indazole part of molecules studied was identified as a sensitive feature for the optimal binding to the receptor with a chlorine at the 3-position of the indazole optimal for high receptor affinity, and this is interesting in developing selective bradykinin B1 receptor antagonists [18]. Hence, the possibility for nigeglanine, in addition to other similar compounds isolated from NG seeds, to provide a starting point for semisynthesis of this kind of interesting compounds since it is one of the rare natural compounds with indazole ring, however this remains to be experimentally proved and investigated. Most recently, four dolabellane-type diterpene alkaloids were isolated for the first time from NG seeds. They were identified as nigellamine A_1, nigellamine A_2, and nigellamine B_1, in addition to nigeglamine, which was a new natural compound [19].

2.2. Flavonoids and Phenolic Compounds. The flavonoids and phenolic compounds isolated from the seeds of this plant include kaempferol; quercetin; rutin; kaempferol-3-*O*-β-D-glucopyranosyl-(1 → 2)-β-D-galactopyranosyl-(1 → 2)-β-D-glucopyranoside; salicylic acid; 4-hydroxybenzoic acid; methyl-4-hydroxybenzoate and pyrogallol [8]. Recently, a new flavonol glycoside, that is, kaempferol 3-*O*-α-L-rhamnopyranosyl (1 → 6)-*O*-[β-D-glucopyranosyl(1 → 2)-*O*-β-D-galactopyranosyl (1 → 2)]-*O*-β-D-glucopyranoside, in addition to a known compound, kaempferol 3-*O*-β-D-glucopyranosyl (1 → 2)-*O*-β-D-galactopyranosyl (1 → 2)-*O*-β-D-glucopyranoside, was isolated from the seeds of NG [8]. Nigeglanoside and nigelloside are flavonoid glycosides also isolated from NG seeds [17, 20].

2.3. Isobenzofuranone Derivatives and Saponins. Two isobenzofuranone derivatives: 5,7-dihydroxy-6-(3-methylbut-2-enyl) isobenzofuran-1(3H)-one and salfredin B11, and two saponins: hederagenin and 3-*O*-[β-D-xylopyranosyl-(1 → 3)-α-L-rhamnopyranosyl-(1 → 2)-α-L-arabinopyranosyl]-hederagenin, were also isolated from the seeds of this Chinese herb [9]. Other saponins (triterpene saponins) isolated from NG seeds include 21β-hydroxyhederagenin; 3-*O*-[β-D-xylopyranosyl-(1 → 3)-α-L-rhamnopyrano-syl-(1 → 2)-α-L-arabinopyranosyl]-hederagenin; 3-*O*-[β-D-xylopyranosyl-(1 → 3)-α-L-rhamnopyranosyl-(1 → 2)-α-L-arabinopyranosyl]-28-*O*-[α-L-rhamnopyranosyl-(1 → 4)-β-D-glucopyranosyl-(1 → 6)-β-D-glucopyranosyl]-hederagenin; 3-*O*-[α-L-rhamnopyranosyl-(1 → 2)-α-L-arabinopyranosyl]-hederagenin-28-*O*-{α-L-rhamnopyranosyl-(1 → 4)-β-D-glucopyranosyl-(1 → 6)-[β-D-xylopyranosyl-(1 → 2)]-β-D-glucopyranosyl ether [10]. Two oleanane triterpene saponins: kalopanaxsaponin A (3-*O*-[L-rhamnopyranosyl-(1 → 2)-α-L-arabinopyranosyl]-hederagenin) and kalopanaxsaponin I (3-*O*-[β-D-xylopyranosyl (1 → 3)-α-L-rhamnopyranosyl-(1 → 2)-α-L-arabinopyranosyl]-hederagenin) [2], were also found in NG seeds. Alpha-hederin is another triterpene saponin isolated from this plant seeds [15].

2.4. Terpenes, Terpenoids, and Similar Compounds. Those reported as being isolated from NG seeds include α-pinene, 1R-α-pinene, sabinene, β-pinene, α-terpinene, τ-terpinene, limonene, Z-β-terpineol (a monoterpene alcohol), fenchene, camphor, carvone, α-longipinene, longifolene, α-bisabolol (a natural monocyclic sesquiterpene alcohol), nerolidol, 4-caraneol, 4-careen, 4-terpineol, and myrtanol [11].

2.5. Fatty Acids. About 35 to 42 percent of NG seeds is oil [6]. An interesting work compared the fatty acid composition of seed oil extracted by Supercritical Carbon Dioxide Extraction (SC-CO_2) and by Soxhlet method. After determination by gas chromatography-mass spectrometry, the results showed that the composition was similar with different extraction methods [6]. This study also showed that the oil contained 12 fatty acids: myristic acid; 9-hexadecenoic acid; heptadecanoic acid; palmitic acid; linoleic acid; oleic acid; 7-octadecenoic acid; stearic acid; 10,13-octadecadienoic acid; arachidic acid; 11,13-eicosadienoic acid; 11-eicosenoic acid. Among them, linoleic acid which is an omega-6 fatty acid was the most abundant unsaturated fatty acid [6]. It is well known that essential fatty acids must be supplied in the diet, required by the human body, and cannot be synthesised endogenously. Therefore, NG seeds oil is a rich nutrition source since it is rich in this essential fatty acid [21]. Linoleic acid has also a platelet aggregation inhibitory potential, which is consistent with the activity believed in folk medicine that NG seeds can stimulate the menstrual flow, and this is possible by activating blood circulation [6, 16]. Oleic acid methyl ester was also isolated from the seeds of NG, which contain also hexacosanoic acid (or cerotic acid), that is, a 26-carbon long-chain saturated fatty acid [22]. In addition, several steroids have been isolated from NG seeds including daucosterol, campesterol, cholesterol, and stigmasterol [20]. Other compounds have also been isolated from NG seeds including m-cymene [11]; p-cymene, thujene [12]; DOP [14]; 1-eicosene [22]; the oligosaccharide nigellamose [20]; ethyl tetradecenyl; 9,12-octadecadien-1-ol; 2, 4 α, 5, 6, 7, 8, 9, 9α-octahydro-benzocycloheptene;

2-propyl-5-oxo-hexanal; 3,7-dimethyl-6-octene-butyl; 2-ethyl-4,5-dimethyl-phenol; 1,3,4-trimethyl-3-cyclohexen-1-formaldehyde; 2,6-dimethyl-3,5,7-oct-3-enol; 3-methyl-1-{3-[5-(3,3-bimethyl-epoxyethyl)]} ethanone; isobornyl acetate [11]. Thymoquinone, which has numerous pharmacogical activities, was also isolated from this amazing herb seeds [11]. The chemical structures of thymoquinone and other selected compounds isolated from NG seeds are shown in Figure 1.

3. Pharmacological Activities and Related Active Compounds

3.1. Antidiabetes and Antiobesity Properties. Non-insulin-dependent diabetes mellitus (NIDDM) fundamental feature is resistance to insulin [12]. Another hormone, leptin, is secreted by adipose tissues throughout the body and its best known function is the appetite feedback control [23]. Recently, many evidences have shown that protein tyrosine phosphatase 1B (PTP1B) is involved in the downregulation of insulin and in leptin signaling [12]. This enzyme is a key element in insulin signaling negative regulation pathway, hence, the importance of its role in diabetes and obesity. Many studies have shown that PTP1B plays a pivotal role in the dephosphorylation of insulin receptors [24]. Hence, it is clear that the inhibition of PTP1B ought to be a potential pharmacological mechanism for the treatment of NIDDM. The potential antidiabetic effect in NG seeds was confirmed based on *in vitro* enzyme assays for protein tyrosine phosphatase inhibitory activities, and furthermore, the most convincing evidence is that PTP1B was involved in the insulin-signaling pathway deriving from the phenotype of the PTP1B knockout (PTP1B KO) mice [12]. These mice (PTP1B−/−) completely deficient in this enzyme showed increasing phosphorylation of insulin receptor, increasing sensitivity to insulin and resistance to diet-induced obesity, and in addition, their growth and development were normal, they were fertile, and were histologically just like wild-type mice (PTP1B+/+) [12, 25–27], thus the importance of PTP1B as a drug target for NIDDM and obesity treatment. Moreover, the difference in chemical constitutes and antidiabetes properties of NG oil extracted by n-hexane (HNG) and petroleum ether (PNG) was investigated [12]. Gas chromatography-mass spectrometry method was used to analyse their chemical components, and different concentrations of PNG and HNG were assayed for their PTPB1 inhibitory effects [12]. The findings showed that, in both of them the unsaturated fatty acids are the main components, there were about 87% in PNG less than them in HNG, and that PNG can inhibit PTP1B with half maximal inhibitory concentration values of 33.15 ± 0.77, against 18.50 ± 0.52 mg/mL for HNG. Thus, it was suggested that not only the unsaturated fatty acids, but also the small molecules compounds, such as p-cymene and thujene, have the predominantly effect in inhibiting PTP1B activity [12].

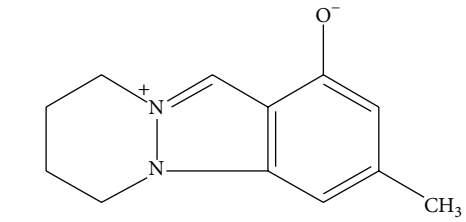
3.2. Skin Depigmenting Properties. Melanin is a brown, yellow-brown, or black pigment produced by melanocytes. These cells manufacture this phenolic biopolymer from the amino acid tyrosine molecules [28]. The melanogenesis is started by the hydroxylation of tyrosine into DOPA, then oxidation of DOPA to dopaquinone; interestingly, this first and rate-limiting step of melanin formation is mediated by tyrosinase, which is the key enzyme required for melanin production [29, 30]. After that, dopaquinone undergoes other multistep pathways to produce melanin [14].

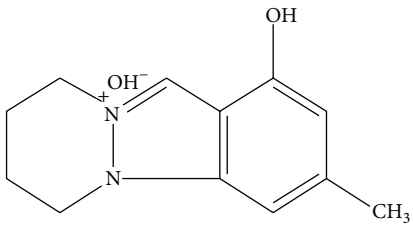
A small amount of ultraviolet (UV) radiation is good for health, because it stimulates synthetic activity in the epidermis, but UV radiation can damage DNA causing mutation and promoting cancer development [28]. Fortunately, the melanin in keratinocytes protects the epidermis and dermis from sunlight harmful effects caused by excessive amounts of UV radiation [28]. However, the increased production and accumulation of melanin in the skin can be the cause of a large number of skin diseases, such as acquired hyperpigmentation that includes melasma, postinflammatory melanoderma, and solar lentigo [14], whereas it was found that there is a variations in human pigmentation among different racial groups because of the differences in the production and deposition of melanin in the skin [29], which may indicate that different races may have different prognoses for such diseases. However, dermatological diseases and their complications have a high frequency in many countries worldwide. Therefore, many researches have been carried out to better understand skin diseases pathways and mechanisms including the biochemical reactions implicated in mammalian melanogenesis [30] and the implication of excessive melanine production in numerous skin and health diseases [31].

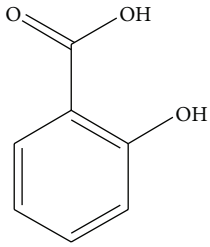
Dermatological diseases not only affect the physical health of the patients, but also may have a psychological effect because of their visible nature [32], and even if the accumulation of melanin just darkens the skin without causing any disease, it may cause an appearance problem for persons not preferring dark skin.

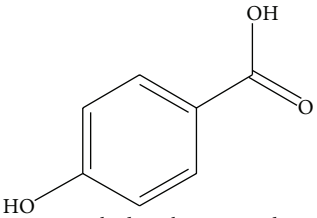
Many melanogenesis inhibitors, which are used as cosmetic additives, are of limited effectiveness, difficult to formulate, or even cause reactions or undesirable effects after long-time usage [14]. Thus, recently, there was more concentration towards the implication of natural products in cosmetics, which are usually characterised by their long-standing safety record [33–35]. NG was one of the Chinese herbal medicines evaluated in order to find safer and more effective inhibitors of melanogenesis as treatments for diseases, or even as skin-whitening agents.

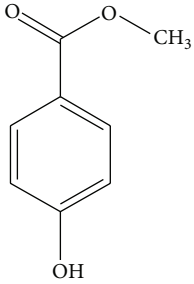
The effect of NG seeds on melanogenesis was investigated, and its methanol extract showed a dose-dependent inhibitory effect on the melanin synthesis of melanoma B16F10 cells [14]. It has been shown that the methanol extract of this plant can inhibit melanogenesis significantly in a dose-dependent manner, and the MTT assay confirmed that the melanin inhibition activity is not caused by cytotoxicity, and methanol extract did not show any toxicity up to 100 μg/mL [14]. In order to identify the compounds involved in the melanin inhibiting effect of the methanol extract, solvent-solvent partition, silica gel open column chromatography, and GC-MS analysis were operated, and it was found that oleic acid methyl ester inhibited melanin synthesis in a dose-dependent manner without toxicity. Because oleic acid methyl ester is

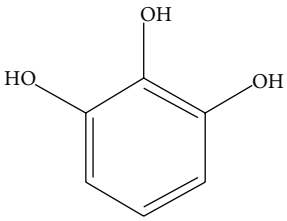

Nigeglanine

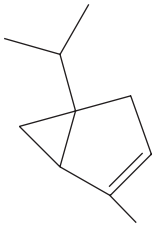

Nigeglapine

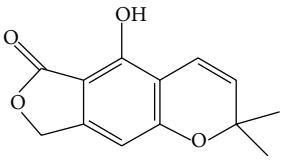

Salicylic acid

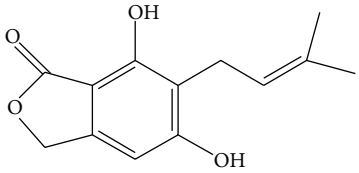

4-hydroxybenzoic acid

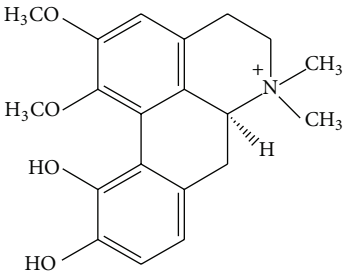

Methyl-4-hydroxybenzoate

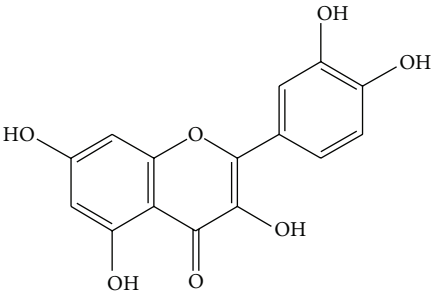

Pyrogallol

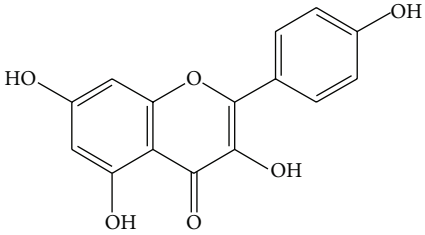

Thujene

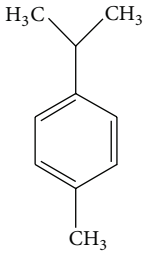

Salfredin B11


5, 7-dihydroxy-6-(3-methybut-2-enyl) isobenzo-furan-1(3H)-one


Fuzitine


Quercetin


Kaempferol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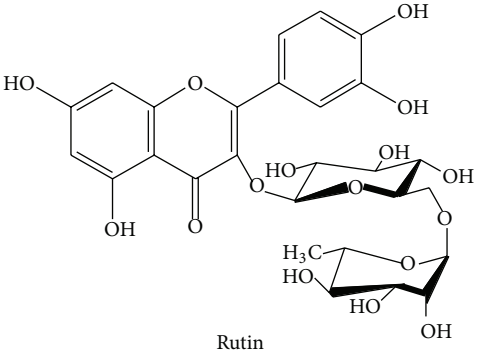
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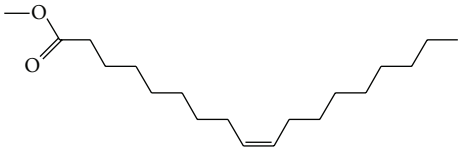
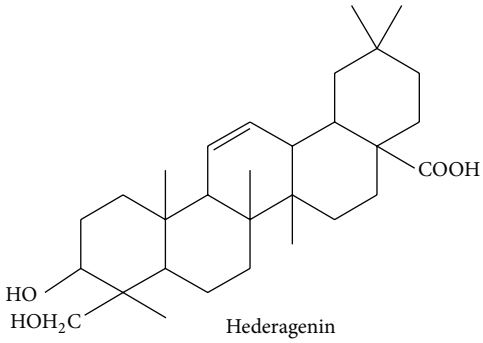
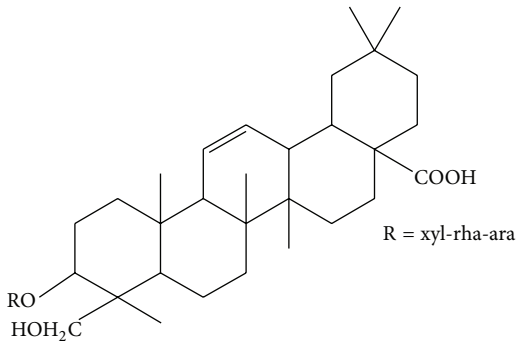

Oleic acid methyl ester

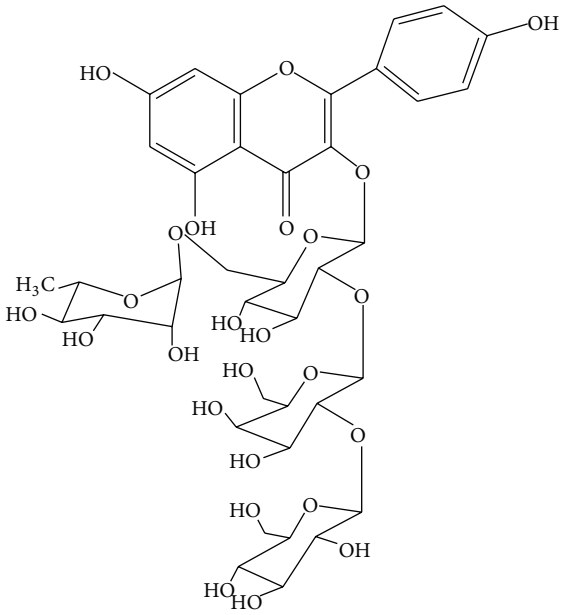
Figure 1: Continued.



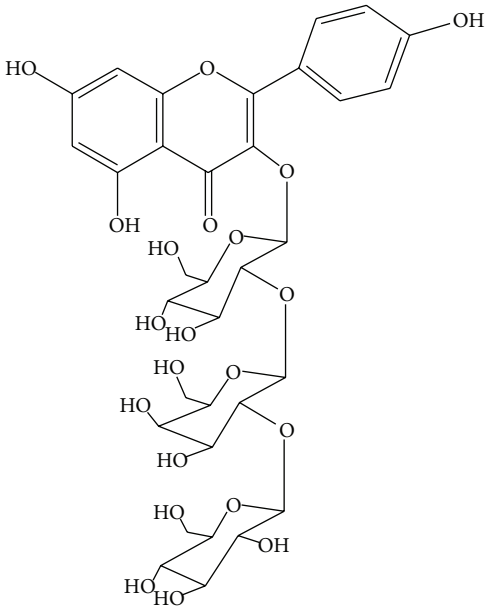
Hederagenin



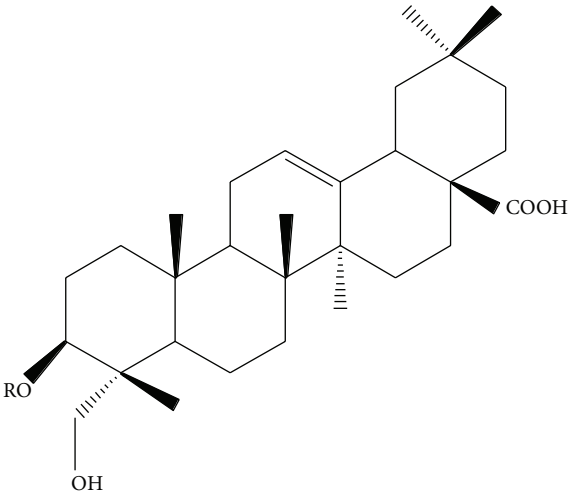
3-*O*-[β-D-xylopyranosyl (1 → 3)-α-L-rhamnopyranosyl-(1 → 2)-α-L-arabinopyranosyl]-hederagenin

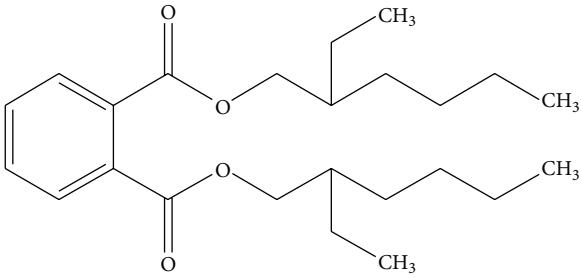


Kaempferol 3-*O*-α-L-rhamnopyranosyl (1 → 6)-*O*-[β-D-glucopyranosyl (1 → 2)-*O*-β-D-galactopyranosyl (1 → 2)]-*O*-β-D-glucopyranoside



Kaempferol 3-*O*-β-D-rhamnopyranosyl (1 → 2)-*O*-β-D-glucopyranosyl (1 → 2)-*O*-β-D-glucopyranoside

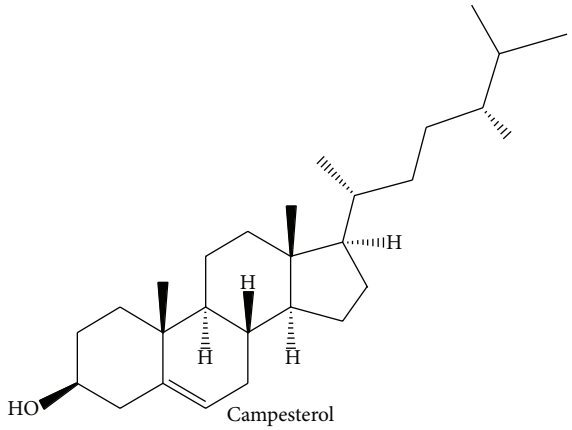


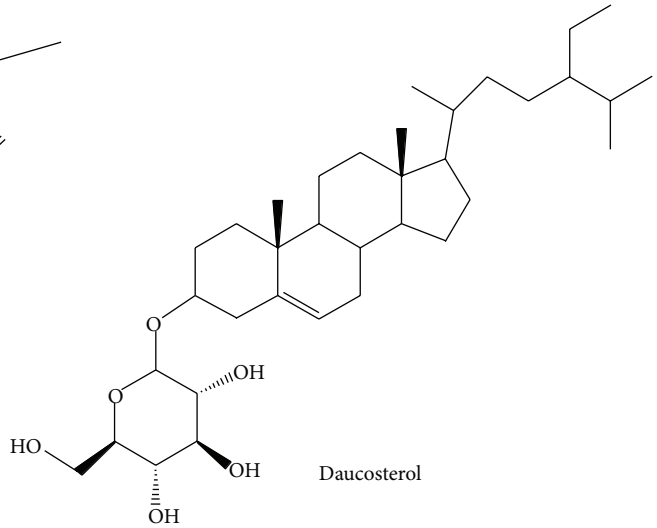


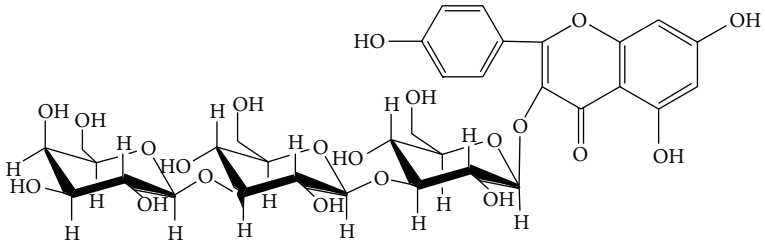
Dioctyl phthalate

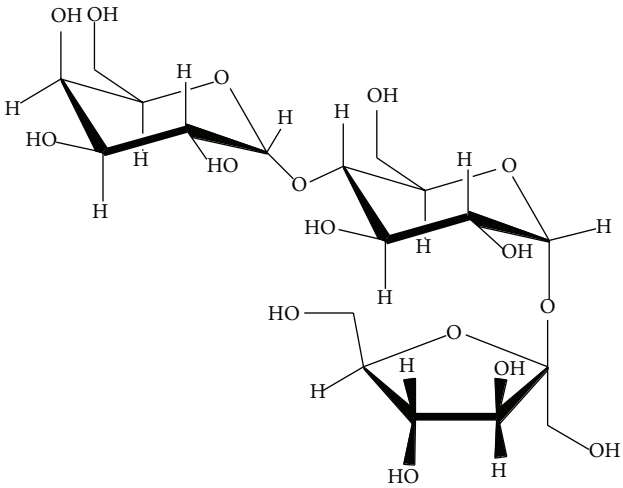
- Kalopanaxsaponin A: R = 3-*O*-[L-rhamnopyranosyl-(1 → 2)-α-L-arabinopyranosyl]-
- Kalopanaxsaponin I: R = 3-*O*-[β-D-xylopyranosyl (1 → 3)-α-L-rhamnopyranosyl-(1 → 2)-α-L-arabinopyranosyl]-

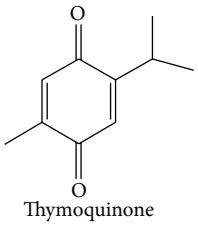
Figure 1: Continued.











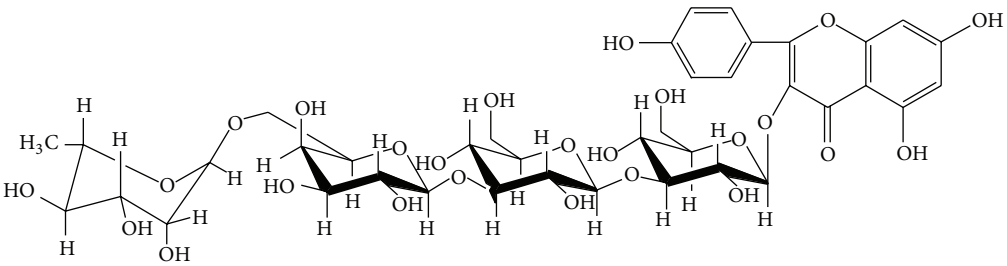


Figure 1: Continued.

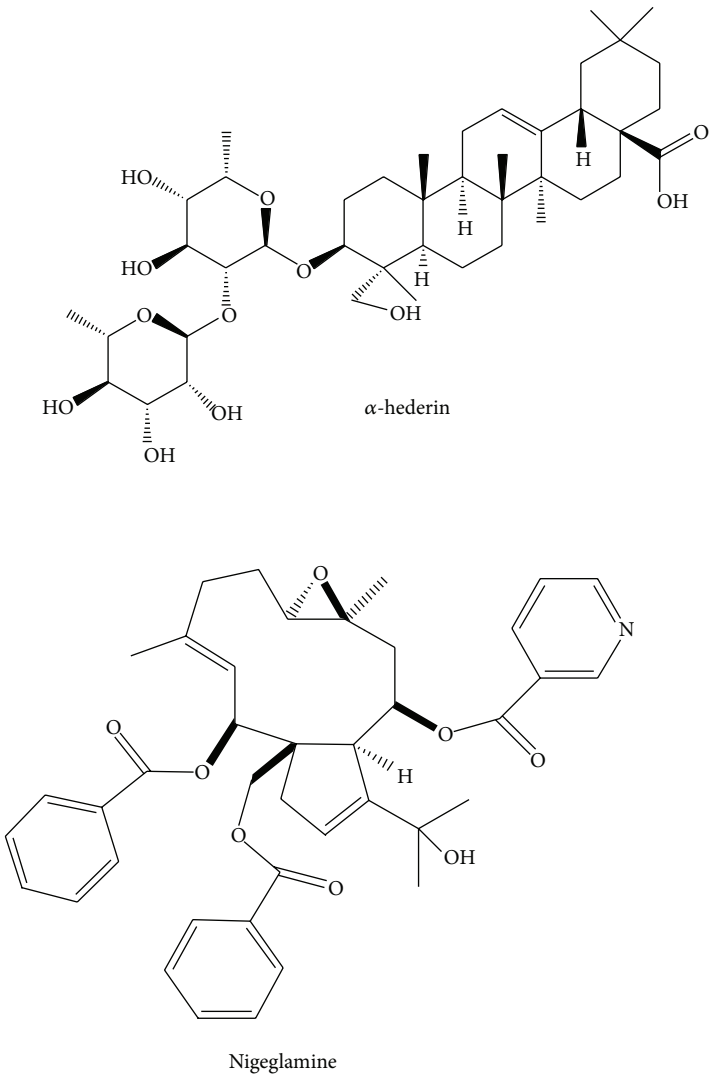


Figure 1: Chemical structures of selected compounds isolated from *Nigella glandulifera* Freyn et Sint seeds.

the main active component in NG seeds, it is expected that the melanin inhibition activity is due to this compound [14]. Another compound that was isolated in NG seeds and presenting an ability to inhibit melanin synthesis by inhibiting the tyrosinase enzyme activity in B16F10 melanoma cells is DOP [14]. Since the methanol extract exhibited some toxicity towards the B16F10 melanoma cells, additional investigations on DOP relation with melanogenesis and its toxicity (MTT assay) have been conducted [14]. They result in finding that this compound had a potent inhibitory effect on the melanogenesis of B16F10 melanoma cells (IC_{50} = 24 μM). Moreover, the compound also showed the same action mode as the crude extract of NG seeds [14]. Although DOP has this inhibition effect of melanogenesis, it was classified as an endocrine disrupter recently, and its use is prohibited [36, 37].

Usually, the presence of DOP in plants results from environmental pollution and many vegetables, such as Chinese tomato fruit that may contain it, and yet the cumulative content is less than 0.01 g/kg fresh weight [38]. Therefore, the higher DOP content in NG seeds may indicate that NG plant possesses a stronger ability to accumulate DOP [14]. It is worth noting that DOP may influence the results as a contaminant of solvents or plants [14]. Moreover, further investigations are suggested to find out other compounds with depigmenting properties, isolated from NG seeds.

3.3. Anticancer Properties. Hepatocellular carcinoma is the most common cancer in many countries [39]. It is also the third leading cause of cancer death because of its very poor prognosis [40]. Although numerous researches are focused on cancer treatment and many drugs are available as anticancer treatments, there is still a serious problem of chemotherapy, that is, multidrug resistance, which may cause the failure of cancer treatment by chemotherapy, in addition to the huge number of anticancer drugs side effects due to the lack of selectivity of anticancer drugs active compounds [2].

These two problems are a great challenge for scientists to find out new drugs which are more selective and having as low toxicity as possible [41]. Two oleanane triterpene saponins: kalopanaxsaponin A (3-O-[L-rhamnopyranosyl-(1 → 2)-α-L-arabinopyranosyl]-hederagenin) and kalopanaxsaponin I (3-O-[β-D-xylopyranosyl (1 → 3)-α-L-rhamnopyranosyl-(1 → 2)-α-L-ara-binopyranosyl]-hederagenin), were isolated from NG seeds in this regard [2]. Previous studies have reported that these two compounds display cytotoxicity in J 82, T 24, Colon 26 and 3LL cancer cells, with IC_{50} values in the range of 1.1–16.5 μM [42]. In addition, kalopanaxsaponin A significantly reduced the LL/2 tumor weight of mice at an intraperitoneal dose of 5–10 mg and apparently prolonged the life span of mice bearing Colon 26 and 3LL Lewis lung carcinomas at 15 mg peritoneal dose [42]. Kalopanaxsaponins A and I isolated from NG seeds cytotoxicity, drug resistance, and their selectivity were evaluated against two liver cell lines cell lines: HepG2, drug resistant HepG2 (R-HepG2) and primary cultured normal mouse hepatocytes [2]. These two compounds showed significant cytotoxic activities towards the two cell lines and primary cultured normal mouse hepatocytes in a concentration-dependent manner [2]. Their cytotoxicities on R-HepG2 were as effective as on HepG2, but the IC_{50} values towards normal mouse hepatocytes were very low; consequently, these two compounds are effective against the drug resistant HepG2 cell line, but had no selective cytotoxicity towards cancer cells [2]. Antitumor properties have also been studied for alpha-hederin. Although it is a commun constituent of NG and NS seeds, in this paper we emphasise the pharmacological activities investigated on NG seeds [43].

There are two different mechanisms of cell death, necrosis and apoptosis, which are different in morphology, mechanism, and incidence [44]. Almost all the cytotoxic antitumor drugs induce apoptosis (programmed cell death), which is an important mechanism to investigate the possible anticancer activity of a compound [2]. The inhibition mechanism for kalopanaxsaponins I and A was investigated through morphological observations and cell cycle analysis, and the findings showed that these two compounds can inhibit hepatoma proliferation by inducing apoptosis, and they may be considered as potential therapeutic agents for the treatment of parental and drug resistant hepatoma [2].

3.4. Anti-Inflammatory Properties. Chronic inflammation is caused by various factors including infections (bacteria, viruses, or parasites), chemical irritants, and nondigestible particles. Since the inflammatory mediators can cause neoplasia, through inducing proneoplastic mutations, adaptive responses, resistance to apoptosis, or environmental changes [45], the development of anti-inflammatory therapy might be an efficient way to fight against cancer. The effect of NG seeds total saponins on inflammatory mediators and ERK/MAPK (extracellular-signal-regulated kinases/mitogen-activated protein kinases) pathway in stimulated macrophages was investigated. In order to study the anti-inflammatory mechanism, interferon-gamma (IFN-γ) plus LPS stimulated RAW 264.7 macrophages were used as inflammatory experimental model. The investigation of NG seeds total saponins anti-inflammatory effect was conducted through several assays [15]. The production of the inflammation molecular mediator nitric oxide (NO), the total antioxidant capacity, mRNA expression, and protein expression examination were performed through Griess diazotization reaction, ferric reducing ability of plasma (FRAP) assay, reverse transcription polymerase chain reaction (RT-PCR), and Western blot, respectively, and the findings were that the saponins inhibited NO production in a dose-dependent manner and suppressed the gene and protein expression of inducible NO synthase (iNOS). This inhibition of NO over production and iNOS expression was possible through ERK/MAPK pathway by noticeable inhibition of the phosphorylation of ERK (pERK) [15]. Furthermore, NG seeds total saponins increased peroxisome proliferators-activated receptor PPAR-γ gene and protein expression, hence the increasing of anti-inflammatory mediators expression, whereas the total saponins contributed to the opposite effect on mRNA of inflammatory mediators, such as COX-2, IL-1β, and IL-6, thus the increasing of the anti-inflammatory effect [15].

3.5. Antithrombosis, Antiplatelet Aggregation, and Ability to Reduce Serum Triglycerides. Among the few studies in this regard, we illustrate two animal experiment examples that have been reported in the literature. To investigate these properties, homemade NG seeds oil emulsion was intragastrically administered to rats by 0.25 g/kg and 0.5 g/kg, with aspirin 0.9 g/kg as positive control drug, for nine days. Then, aortic blood was drew from each rat's abdomen, and platelet rich plasma (PRP) and poor platelet plasma (PPP) were prepared through centrifugation. Adenosine diphosphate (ADP) and collagen were used as inducers, and platelet aggregation was determined automatically with a turbidimetric method. Both of the two doses of NG seeds oil inhibited the induced rat platelet aggregation significantly [46]. Another work was also conducted to study this effect, and rats were divided into five groups: two groups were the control and the model group, respectively, and for the other three groups, rats were administered aspirin intragastrically by 0.3 g/kg, NG seed oil by 0.5 g/kg, and 1.0 g/kg, respectively. The rats were administered the drugs for nine days successively, but they were administered cholesterol two days before. After the last administration of the drug, the rat's abdomen aortic blood was drew for blood clots experiment. It was found that NG seeds oil can significantly inhibit *in vitro* thrombosis of rats. The content of triglycerides and cholesterol in blood samples was also determined, and it was found that NG seeds oil can reduce the production of triglycerides, but no obvious effect on reducing cholesterol content has been noticed. Since the linoleic acid accounts for 55.35% in NG seed oil, it was suggested that it is the active ingredient in NG seeds oil that has the antithrombosis and antiplatelet aggregation effects, in addition to the ability to reduce the serum triglycerides. These results converge with the pharmacological activities believed in folk medicine [16].

4. Conclusions and Future Perspectives

Numerous plants are used in folk medicine and are popular worldwide. However, further investigations and clinical studies are still required to find out the active compounds, activity mechanisms, and possible toxicity; for instance, although NG belongs to the same family (Ranunculaceae) and the same genus as NS, researches focusing on the former are still lacking, compared to the latter. Furthermore, these two species seeds contain a number of similar and common compounds; for example, the alkaloids nigellicine and nigellidine were isolated from the seeds of NS and NG. Nigeglanine, with a special indazole ring, is another alkaloid isolated from NG seeds, which presents a chemical structure similarity with nigellicine and nigellidine due to the common indazole ring. Thymoquinone has also been isolated from both NG and NS seeds, and interestingly, this molecule has been described in a tremendous number of papers as a major bioactive component of NS seeds oil that affords a miraculous power of healing. The anti-inflammatory and anticancer properties of thymoquinone isolated from NS have been proven *in vitro* and *in vivo*. Moreover, other properties have also been reported as a potential treatment for various disease models including diabetes, asthma, and encephalomyelitis. Furthermore, this molecule could act as a free radical, superoxide radical scavenger, and preservation agent of various antioxidant enzymes activity, such as catalase, glutathione peroxidase, and glutathione-S-transferase [47]. Alpha-hederin is another common constituent of NG and NS seeds. Studies have concluded that it has both hemolytic and antifungal activities [48]. It has also a P450 suppression potential, which is apparently one of the mice protective mechanisms against chemicals-induced hepatotoxicity [49]. It has also been investigated for its antitumor activity [43]. However, these activities need deeper investigations, hence, the importance of conducting more studies not only on NS, which is described as a miracle herb [50], but also on NG seeds extracts that contain these active compounds. Nigellamine A_1, nigellamine A_2, and nigellamine B_1 are also common constituents of these two species seeds [51]. They were isolated recently from NG seeds and are already known as constituents of NS seeds. These common compounds and other common constituents may reflect the potential similarity of pharmacological healing properties, which might be very useful for regions where NG is more available than NS.

Among the pharmacological activities of NS seeds oil and thymoquinone that were found out through researches on NS seeds are their protective effects on lipid peroxidation process during cerebral ischemia-reperfusion injury in rat hippocampus [52], their antinociceptive effects through indirect activation of the supraspinal mu(1)- and kappa-opioid receptor subtypes in mice [53], and thymoquinone possible anticonvulsant activity in the petit mal epilepsy (probably through an opioid receptor-mediated increase in GABAergic tone) [54]. Furthermore, on the basis of the structural similarity between compounds isolated from these two plants seeds, the similarity of their range of target diseases believed in folk medicine, and the fact that many therapeutical actions believed in folk medicine for NS seeds have been proven experimentally, and we strongly suggest that further research on NG seeds would be highly promising. Researches on NS seeds provide useful orientations for researchers towards elucidating the action mechanisms and thus finding out scientific explanations of NG seeds against numerous diseases. Therefore, we encourage conducting experiments on NG seeds on the basis of those carried out on NS seeds. We further suggest the study of the pharmacological activities that are already applied in folk medicine. Indeed, among the numerous studies and pharmacological properties investigated in NS seeds, we mention some selected examples. In pulmonology, the investigations included the study of the effects of NS seeds extract on ameliorating lung tissue damage in rats after experimental pulmonary aspirations [55], the considerable ability of NS oil to reduce the severity of lung damage due to hyperoxia [56], the ameliorative effect of NS oil on ovalbumin-induced bronchial asthma in mice [57], and NG potential ability of treating allergic rhinitis as an alternative when the effects of other antiallergic drugs need to be avoided [58]. In microbiology, the protective effect of NS oil against murine cytomegalovirus infection [59] and the antimicrobial activity of diethyl ether extract of NS seeds against Gram-positive and Gram-negative bacteria have been studied [60]. The effect of NS seeds oil against liver damage induced by *Schistosoma mansoni* infection in mice [61] was also investigated. NS ability to improve lipid profile and to prevent atherosclerosis in rabbits was also the subject for other studies [62]. Other researches focused on the protective effects of NS against gentamicin-induced nephrotoxicity in rats [63]. Experimental investigations have also been conducted to study NS aqueous and ethanolic extracts ability to stimulate milk production in rats [64]. Furthermore, NS oil protective action against gastric secretion and ethanol-induced ulcer in rats [65], NS seeds volatile oil antioxytocic potential [66], the anti-inflammatory, the antipyretic activity of NS [67], and NS seeds effects on the central nervous system (CNS) and on analgesic activity [68] have also been studied. For all the mentioned examples, the results were highly encouraging and promising. The mentioned publications about NS in addition to other studies represent potential starting points to further the research on NG, which has an underestimated value despite the fact that NG and NS have been applied to treat almost the same diseases in folk medicine.

Further *in vitro* and *in vivo* investigations on NG seeds appear very promising, especially because of that the efficacy of this plants seeds on serious health problems, such as cancer, diabetes, thrombosis, and inflammation has been proven. NG seeds compounds could be a vital solution and even may suggest a whole food profile able to reduce NIDDM-induced pathogenesis directly, and indirectly through treating obesity problem. NG seeds represent a promising source of skin-whitening and antiobesity agents. These seeds constitute also a good source of unsaturated fatty acids, hence, the importance of their oil within healthy diet.

NG seeds might constitute a straight orientation on the right way to make a substantial amelioration in divers fields

including nutrition, pharmacy, and aesthetics. However, further laboratory investigations and clinical studies remain highly required to investigate the safety and the toxicological profile of the isolated compounds, their *in vivo* efficacy, and their possible undesirable side effects. Moreover, further studies should be carried out to ensure the quality and the sustainability in regard of this amazing plant, which is highly promising to get a place among the scientifically top-rated herbal medicines. In addition, we noticed that most of the published studies about NG have been conducted in China, especially west of China, and also in Korea. That is probably because of the historical and traditional use of NG in these two countries. However, collaborative research between divers countries' laboratories is recommended to generate reproducible results and to enlarge the research scale and enhance the chances of isolating novel compounds from this promising plant, and then scientifically prove the related activities that are believed and used in folk medicine.

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References

[1] Y. M. Liu, J. S. Yang, and Q. H. Liu, "A new alkaloid and its artificial derivative with an indazole ring from *Nigella glandulifera*," *Chemical and Pharmaceutical Bulletin*, vol. 52, no. 4, pp. 454–455, 2004.

[2] Z. Tian, Y. M. Liu, S. B. Chen et al., "Cytotoxicity of two triterpenoids from *Nigella glandulifera*," *Molecules*, vol. 11, no. 9, pp. 693–699, 2006.

[3] G. P. Sagitullina, A. K. Garkushenko, N. V. Poendaev, and R. S. Sagitullin, "Simple and efficient synthesis of substituted 1H-indazoles," *Mendeleev Communications*, vol. 22, no. 3, pp. 167–168, 2012.

[4] G. E. Buchel, I. N. Stepanenko, M. Hejl et al., "Osmium(IV) complexes with 1H- and 2H-indazoles: tautomer identity versus spectroscopic properties and antiproliferative activity," *Journal of Inorganic Biochemistry*, vol. 113, pp. 47–54, 2012.

[5] Y. Zhang, D. Ge, Q. Chen et al., "Flavonol glycosides, nigelflavonosides A-F from the whole plant of *Nigella glandulifera* (Ranunculaceae)," *Journal of Natural Medicines*, vol. 66, pp. 645–652, 2012.

[6] J. P. Zhang, X. L. Hou, T. Yu, Y. Li, and H. Y. Dong, "Response surface optimization of *Nigella glandulifera* freyn seed oil yield by supercritical carbon dioxide extraction," *Journal of Integrative Agriculture*, vol. 11, no. 1, pp. 151–158, 2012.

[7] X. L. Xin, H. A. Aisa, and H. Q. Wang, "Flavonoids and phenolic compounds from seeds of the Chinese plant *Nigella glandulifera*," *Chemistry of Natural Compounds*, vol. 44, no. 3, pp. 368–369, 2008.

[8] Y. M. Liu, Q. H. Liu, and B. Q. Chen, "A new flavonol glycoside from the seeds of *Nigella glandulifera*," *Natural Product Research*, vol. 25, no. 14, pp. 1334–1338, 2011.

[9] X. Xin, Y. Yang, J. Zhong, H. A. Aisa, and H. Wang, "Preparative isolation and purification of isobenzofuranone derivatives and saponins from seeds of *Nigella glandulifera* Freyn by high-speed counter-current chromatography combined with gel filtration," *Journal of Chromatography A*, vol. 1216, no. 19, pp. 4258–4262, 2009.

[10] X. L. Xin, H. A. Aisa, H. Q. Xue, and H. Q. Wang, "Triterpene saponins from seeds of the Chinese plant *Nigella glandulifera*," *Chemistry of Natural Compounds*, vol. 44, no. 1, pp. 134–136, 2008.

[11] D. Geng, S. Zhang, and J. Lan, "Analysis on chemical components of volatile oil and determination of thymoquinone from seed of *Nigella glandulifera*," *Zhongguo Zhongyao Zazhi*, vol. 34, no. 22, pp. 2887–2890, 2009.

[12] X. Xin, Q. Wang, H. A. Aisa, and H. Wang, "Antidiabetes properties of n-hexane and petroleum ether extracts from seeds of *Nigella glandulifera* freyn," *Journal of Food Biochemistry*, vol. 34, no. 4, pp. 811–824, 2010.

[13] D. H. Nguyen, J. E. Lee, and E. K. Kim, "Identification of depigmenting components from *Nigella glandulifera* Freyn," *Korean Journal of Chemical Engineering*, vol. 28, no. 4, pp. 1070–1073, 2011.

[14] D. T. M. Nguyen, D. H. Nguyen, H. L. Lyun, H. B. Lee, J. H. Shin, and E. K. Kim, "Inhibition of melanogenesis by dioctyl phthalate isolated from *Nigella glandulifera* Freyn," *Journal of Microbiology and Biotechnology*, vol. 17, no. 10, pp. 1585–1590, 2007.

[15] D. Zhang, X. Nie, H. Pan et al., "Study on effect of total saponins from Semen Nigellae on inflammatory mediators and ERK/MAPK pathway in stimulated macrophage," *Zhongguo Zhongyao Zazhi*, vol. 35, no. 19, pp. 2594–2598, 2010.

[16] D. S. Geng and X. Y. Fu, "The status of pharmacological research and chemical constituents of *Nigella glandulifera*," *Chinese Traditional Patent Medicine*, vol. 30, no. 10, pp. 1522–1524, 2008.

[17] X. G. Jia, L. Pan, X. J. Li, S. J. Jia, and M. Bolati, "Progress in chemical composition of Nigella," in *Proceedings of the 9th National Symposium on Natural Medicinal Material Resources*, pp. 504–506, 2010.

[18] V. Bodmer-Narkevitch, N. J. Anthony, V. Cofre et al., "Indazole derivatives as novel bradykinin B1 receptor antagonists," *Bioorganic and Medicinal Chemistry Letters*, vol. 20, no. 23, pp. 7011–7014, 2010.

[19] Y. M. Liu, L. Sun, Q. H. Liu, S. R. Lu, and B. Q. Chen, "Dolabellane-type diterpene alkaloids from *Nigella glandulifera*," *Biochemical Systematics and Ecology*, vol. 49, pp. 43–46, 2013.

[20] A. Ainiwaer, M. Guli, J. G. Li, and Y. Wang, "Components of xinjiang uyghur medicine *Nigella glandulifera* seed," *Shanghai Journal of Traditional Chinese Medicine*, vol. 42, no. 9, article 73, 2008.

[21] E. N. Smit, F. A. J. Muskiet, and E. R. Boersma, "The possible role of essential fatty acids in the pathophysiology of malnutrition: a review," *Prostaglandins Leukotrienes and Essential Fatty Acids*, vol. 71, no. 4, pp. 241–250, 2004.

[22] Y. M. Liu, J. S. Yang, and Q. H. Liu, "Studies on chemical constituents in the seeds of *Nigella glandulifera*," *Journal of Medicine & Pharmacy of Chinese Minorities*, vol. 9, no. 9, pp. 36–37, 2008.

[23] F. H. Martini, W. C. Ober, C. W. Garrison, K. Welch, and R. T. Hutchings, "The endocrine tissues of other systems," in *Fundamentals of Anatomy and Physiology*, chapter 18, p. 609, Prentice-Hall, Upper Saddle River, NJ, USA, 5th edition, 2001.

[24] J. C. H. Byon, A. B. Kusari, and J. Kusari, "Protein-tyrosine phosphatase-1B acts as a negative regulator of insulin signal transduction," *Molecular and Cellular Biochemistry*, vol. 182, no. 1-2, pp. 101–108, 1998.

[25] M. Elchebly, P. Payette, E. Michaliszyn et al., "Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase-1B gene," *Science*, vol. 283, no. 5407, pp. 1544–1548, 1999.

[26] C. M. Rondinone, J. M. Trevillyan, J. Clampit et al., "Protein tyrosine phosphatase 1B reduction regulates adiposity and expression of genes involved in lipogenesis," *Diabetes*, vol. 51, no. 8, pp. 2405–2411, 2002.

[27] B. A. Zinker, C. M. Rondinone, J. M. Trevillyan et al., "PTP1B antisense oligonucleotide lowers PTP1B protein, normalizes blood glucose, and improves insulin sensitivity in diabetic mice," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 99, no. 17, pp. 11357–11362, 2002.

[28] F. H. Martini, W. C. Ober, C. W. Garrison, K. Welch, and R. T. Hutchings, "The epidermis," in *Fundamentals of Anatomy and Physiology*, chapter 5, pp. 147–148, Prentice-Hall, Upper Saddle River, NJ, USA, 5th edition, 2001.

[29] K. Iozumi, G. E. Hoganson, R. Pennella, M. A. Everett, and B. B. Fuller, "Role of tyrosinase as the determinant of pigmentation in cultured human melanocytes," *Journal of Investigative Dermatology*, vol. 100, no. 6, pp. 806–811, 1993.

[30] A. Korner and J. Pawelek, "Mammalian tyrosinase catalyzes three reactions in the biosynthesis of melanin," *Science*, vol. 217, no. 4565, pp. 1163–1165, 1982.

[31] K. Urabe, J. Nakayama, and Y. Hori, "Mixed epidermal and dermal hypermelanoses," in *The Pigmentary System: Physiology and Pathophysiology*, J. J. Norlund, R. E. Boissy, V. J. Hearing, R. A. King, and J. P. Ortonne, Eds., pp. 909–911, Oxford University Press, Oxford, Miss, USA, 1st edition, 1998.

[32] B. Halioua, M. G. Beumont, and F. Lunel, "Quality of life in dermatology," *International Journal of Dermatology*, vol. 39, no. 11, pp. 801–806, 2000.

[33] S. Baek, D. Kim, C. Lee, Y. Kho, and C. Lee, "Idescarpin isolated from the fruits of Idesia polycarpa inhibits melanin biosynthesis," *Journal of Microbiology and Biotechnology*, vol. 16, no. 5, pp. 667–672, 2006.

[34] W. G. Kim, I. J. Ryoo, S. H. Park et al., "Terrein, a melanin biosynthesis inhibitor, from Penicillium sp. 20135," *Journal of Microbiology and Biotechnology*, vol. 15, no. 4, pp. 891–894, 2005.

[35] Y. H. Lim, I. H. Kim, J. J. Seo, and J. K. Kim, "Tyrokinase inhibitor from the flowers of impatiens balsamina," *Journal of Microbiology and Biotechnology*, vol. 16, no. 12, pp. 1977–1983, 2006.

[36] S. Sekiguchi, S. Ito, M. Suda, and T. Honma, "Involvement of thyroxine in ovarian toxicity of di-(2-ethylhexyl) phthalate," *Industrial Health*, vol. 44, no. 2, pp. 274–279, 2006.

[37] J. A. Tickner, T. Schettler, T. Guidotti, M. McCally, and M. Rossi, "Health risks posed by use of Di-2-ethylhexyl phthalate (DEHP) in PVC medical devices: a critical review," *American Journal of Industrial Medicine*, vol. 39, no. 1, pp. 100–111, 2001.

[38] Q. Du, L. Shen, L. Xiu, G. Jerz, and P. Winterhalter, "Di-2-ethylhexyl phthalate in the fruits of Benincasa hispida," *Food Additives and Contaminants*, vol. 23, no. 6, pp. 552–555, 2006.

[39] F. X. Bosch, J. Ribes, and J. Borràs, "Epidemiology of primary liver cancer," *Seminars in Liver Disease*, vol. 19, no. 3, pp. 271–285, 1999.

[40] N. Abdel-Hamid, "Update to risk factors for hepatocellular carcinoma," *International Journal of Medicine and Medical Sciences*, vol. 1, no. 3, pp. 038–043, 2009.

[41] W. N. Setzer and M. C. Setzer, "Plant-derived triterpenoids as potential antineoplastic agents.," *Mini Reviews in Medicinal Chemistry*, vol. 3, no. 6, pp. 540–556, 2003.

[42] H. J. Park, S. H. Kwon, J. H. Lee, K. H. Lee, K. I. Miyamoto, and K. T. Lee, "Kalopanaxsaponin A is a basic saponin structure for the anti-tumor activity of hederagenin monodesmosides," *Planta Medica*, vol. 67, no. 2, pp. 118–121, 2001.

[43] S. S. Muthu Kumara and B. T. Kwong Huat, "Extraction, isolation and characterisation of antitumor principle, α-hederin, from the seeds of *Nigella sativa*," *Planta Medica*, vol. 67, no. 1, pp. 29–32, 2001.

[44] C. Dive, C. D. Gregory, D. J. Phipps, D. L. Evans, A. E. Milner, and A. H. Wyllie, "Analysis and discrimination of necrosis and apoptosis (programmed cell death) by multiparameter flow cytometry," *Biochimica et Biophysica Acta*, vol. 1133, no. 3, pp. 275–285, 1992.

[45] E. Shacter and S. A. Weitzman, "Chronic inflammation and cancer," *Oncology*, vol. 16, no. 2, pp. 217–230, 2002.

[46] J. Z. Guo, H. F. Hao, L. J. Ren, K. M. Li, and L. Zhang, "Effects of *Neiglla glanelulifera* oil on rat thrombus formation and platelet aggregation," *Pharmacology and Clinics of Chinese Materia Medica*, vol. 16, no. 5, pp. 20–21, 2000.

[47] C. C. Woo, A. P. Kumar, G. Sethi, and K. H. Tan, "Thymoquinone: potential cure for inflammatory disorders and cancer," *Biochemical Pharmacology*, vol. 83, no. 4, pp. 443–451, 2012.

[48] M. Takechi and T. Yasuo, "Structure-activity relationships of the saponin α-hederin," *Phytochemistry*, vol. 29, no. 2, pp. 451–452, 1990.

[49] J. Liu, Y. Liu, P. Bullock, and C. D. Klaassen, "Suppression of liver cytochrome P450 by α-hederin: relevance to hepatoprotection," *Toxicology and Applied Pharmacology*, vol. 134, no. 1, pp. 124–131, 1995.

[50] A. Aftab, H. Asif, M. Mohd et al., "A review on therapeutic potential of *Nigella sativa*: a miracle herb," *Asian Pacific Journal of Tropical Biomedicine*, vol. 3, no. 5, pp. 337–352, 2013.

[51] T. Morikawa, F. Xu, Y. Kashima, H. Matsuda, K. Ninomiya, and M. Yoshikawa, "Novel dolabellane-type diterpene alkaloids with lipid metabolism promoting activities from the seeds of *Nigella sativa*," *Organic Letters*, vol. 6, no. 6, pp. 869–872, 2004.

[52] H. Hosseinzadeh, S. Parvardeh, M. N. Asl, H. R. Sadeghnia, and T. Ziaee, "Effect of thymoquinone and *Nigella sativa* seeds oil on lipid peroxidation level during global cerebral ischemia-reperfusion injury in rat hippocampus," *Phytomedicine*, vol. 14, no. 9, pp. 621–627, 2007.

[53] A. F. M. Abdel-Fattah, K. Matsumoto, and H. Watanabe, "Antinociceptive effects of *Nigella sativa* oil and its major component, thymoquinone, in mice," *European Journal of Pharmacology*, vol. 400, no. 1, pp. 89–97, 2000.

[54] H. Hosseinzadeh and S. Parvardeh, "Anticonvulsant effects of thymoquinone, the major constituent of *Nigella sativa* seeds, in mice," *Phytomedicine*, vol. 11, no. 1, pp. 56–64, 2004.

[55] M. Kanter, "Effects of *Nigella sativa* seed extract on ameliorating lung tissue damage in rats after experimental pulmonary aspirations," *Acta Histochemica*, vol. 111, no. 5, pp. 393–403, 2009.

[56] C. Tayman, F. Cekmez, I. M. Kafa et al., "Effects of *Nigella sativa* oil in hyperoxia-induced lung injury," *Archivos de Bronconeumología*, vol. 49, no. 1, pp. 15–21, 2013.

[57] M. F. Balaha, H. Tanaka, H. Yamashita, M. N. Abdel Rahman, and N. Inagaki, "Oral *Nigella sativa* oil ameliorates ovalbumin-induced bronchial asthma in mice," *International Immunopharmacology*, vol. 14, no. 2, pp. 224–231, 2012.

[58] S. Nikakhlagh, F. Rahim, F. H. Aryani, A. Syahpoush, M. G. Brougerdnya, and N. Saki, "Herbal treatment of allergic rhinitis: the use of *Nigella sativa*," *American Journal of Otolaryngology*, vol. 32, no. 5, pp. 402–407, 2011.

[59] M. L. Salem and M. S. Hossain, "Protective effect of black seed oil from *Nigella sativa* against murine cytomegalovirus infection," *International Journal of Immunopharmacology*, vol. 22, no. 9, pp. 729–740, 2000.

[60] M. S. M. Hanafy and M. E. Hatem, "Studies on the antimicrobial activity of *Nigella sativa* seed (black cumin)," *Journal of Ethnopharmacology*, vol. 34, no. 2-3, pp. 275–278, 1991.

[61] M. R. Mahmoud, H. S. El-Abhar, and S. Saleh, "The effect of *Nigella sativa* oil against the liver damage induced by Schistosoma mansoni infection in mice," *Journal of Ethnopharmacology*, vol. 79, no. 1, pp. 1–11, 2002.

[62] S. Asgarya, A. Ghannadib, G. Dashtic, A. Helalatc, A. Sahebkard, and S. Najafie, "*Nigella sativa* L. improves lipid profile and prevents atherosclerosis: evidence from an experimental study on hypercholesterolemic rabbits," *Journal of Functional Foods*, vol. 5, no. 1, pp. 228–234, 2013.

[63] I. Yaman and E. Balikci, "Protective effects of *Nigella sativa* against gentamicin-induced nephrotoxicity in rats," *Experimental and Toxicologic Pathology*, vol. 62, no. 2, pp. 183–190, 2010.

[64] H. Hosseinzadeh, M. Tafaghodi, M. J. Mosavi, and E. Taghiabadi, "Effect of aqueous and ethanolic extracts of *Nigella sativa* seeds on milk production in rats," *Journal of Acupuncture and Meridian Studies*, vol. 6, no. 1, pp. 18–23, 2013.

[65] M. El-Dakhakhny, M. Barakat, M. Abd El-Halim, and S. M. Aly, "Effects of *Nigella sativa* oil on gastric secretion and ethanol induced ulcer in rats," *Journal of Ethnopharmacology*, vol. 72, no. 1-2, pp. 299–304, 2000.

[66] M. Aqel and R. Shaheen, "Effects of the volatile oil of *Nigella sativa* seeds on the uterine smooth muscle of rat and guinea pig," *Journal of Ethnopharmacology*, vol. 52, no. 1, pp. 23–26, 1996.

[67] M. S. Al-Ghamdi, "The anti-inflammatory, analgesic and antipyretic activity of *Nigella sativa*," *Journal of Ethnopharmacology*, vol. 76, no. 1, pp. 45–48, 2001.

[68] T. B. Al-Naggar, M. P. Gómez-Serranillos, M. E. Carretero, and A. M. Villar, "Neuropharmacological activity of *Nigella sativa* L. extracts," *Journal of Ethnopharmacology*, vol. 88, no. 1, pp. 63–68, 2003.