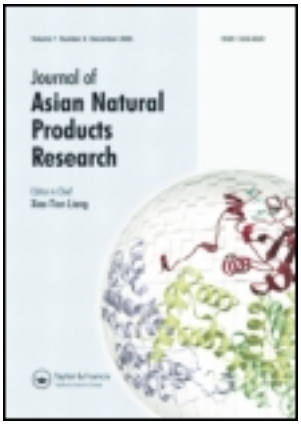

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Reviews on 1,4-naphthoquinones from *Diospyros* L.

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Reviews on 1,4-naphthoquinones from *Diospyros* L.

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The genus *Diospyros* is one of the most important sources of bioactive compounds, exclusively 1,4-naphthoquinones. The following information is an attempt to cover the developments in the biology and phytochemistry of 1,4-naphthoquinones isolated from this genus, as well as the studies done and the suggested mechanisms regarding their activities. During the past 60 years, many of these agents have been isolated from *Diospyros* L. Twelve considerable bioactive structures are reported in this review. The basic 1,4-naphthoquinone skeletons, on which a large number of studies have been done, are plumbagin and diospyrin. Today, the potential for development of leads from 1,4-naphthoquinones obtained from *Diospyros* L. is growing dramatically, mainly in the area of anticancer and antibacterial investigations. The data prepared and described here are intended to be served as a reference tool to the natural products and chemistry specialists in order to expand the rational drug design.

Keywords: *Diospyros*; 1,4-naphthoquinone; antibacterial; anticancer; mechanism

1. Introduction

The family Ebenaceae Gürke consists of six genera (*Diospyros*, *Euclea*, *Lissocarpa*, *Maba*, *Royena*, and *Tetraclis*), and approximately more than 500 species of evergreen trees and shrubs [1,2]. Among all these genera, the genus *Diospyros* has been the most studied [3–5]. The genus of *Lissocarpa* Benth. includes eight species which are found mostly in America [6]. The genus of *Maba* J.R. Forst. & G. Forst. consists of around 50 species found in southeast Africa [7]. The genera of *Royena* L. and *Tetraclis* Hiern. are made of around 15 species and one species, respectively, which are found in subtropic and tropical southeast Asia and South Africa [8]. The *Euclea* L. genus consists of about 20 species of evergreen trees and shrubs, found in southern Africa, the Comoro Islands, and Arabia [9]. The genus *Diospyros* (persimmon, ebony) with about 400–500 species is the largest genus in the Ebenaceae family. This genus is mainly concentrated in the tropical zones, with few species found in temperate regions [10,11]. Many plants belonging to the *Diospyros* L. are used in folk medicine for various purposes. The study of biological and pharmacological assays of *Diospyros* L. started in the early 1950s [12–18]. Some of their extracts have been used in herbal medicines market [19]. Moreover, during these years, there were many studies done on single isolated compounds from Diospyros [20]. 1,4-Naphthoquinone is one of the outstanding chemical structures of *Diospyros* L. and has displayed a broad array of biological effects such as anthelmintic, antifungal,

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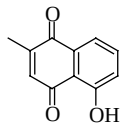
antihypertensive, antibacterial, and antidiarrhea [21–26]. 1,4-Naphthoquinone forms the primary skeleton chemical structure of many natural compounds. On account of their chemical structure stability, 1,4-naphthoquinone agents are recognized for antibacterial and anticancer activities [27–29]. Besides, based on the main principals of drug discovery, it is clear that by means of quantitative structure–activity relationship, medicinal chemistry, and semi-synthesis techniques, these isolated compounds can be useful in drug development [30–33]. Therefore, in this review, chemical structures, sources, and suggested mechanisms of 12 distinguished biologically and pharmacologically active 1,4-naphthoquinones isolated from *Diospyros* L. are discussed in order to illustrate the potency of this genus as a bioresource for tomorrow's drug discovery (Figure 1).

2. Bioactive 1,4-naphthoquinones from the genus *Diospyros*

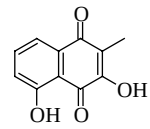
The genus of *Diospyros* L. is a rich source of naphthoquinones [34]. All these naphthoquinones belong to the class of natural phenols based on having the C6-C4 skeleton [35]. About 80% of naphthoquinones of this genus are composed of 1,4 naphthoquinones (around 60 of these compounds have been reported). They consist mostly of monomers and dimers, although few of them are trimers and tetramers [20,36]. Here, the main and crucial characteristics of considerably tested active 1,4-naphthoquinone compounds are described.

5-Hydroxy-2-methyl-1,4-naphthoquinone called plumbagin (**1**) was isolated from *D. hebecarpa* A. Cunn. ex Benth. in 1952 as the first active compound of this genus [37]. This compound was also isolated from other *Diospyros* species [38–43]. One of the unique properties of this agent is the antibacterial activity. It manifests magnificent effects against both gram positive and negative bacteria [44]. The other bioactivity of this compound is the anticancer effect. There are some investigations done on *Diospyros* L. which have introduced plumbagin as a potent cytotoxic agent [45]. Plumbagin is the primary skeleton of many monomeric and oligomeric naphthoquinones [46–55]. Droserone (**2**, 3-hydroxyl plumbagin was isolated from *D. maritima* Blume. and the heartwood part of *D. melanoxylon* Roxb. [56]. It showed moderated cytotoxic activity against MCF-7 cell lines ($IC_{50} = 0.29\,\mu g/ml$) [57]. The 7-methyljuglone (**3**) is one of the main skeletons of monomeric and oligomeric 1,4-naphthoquinones which was isolated from *D. hebecarpa* A. Cunn. ex Benth. for the first time [36]. Later, it was isolated from other species of this genus [58–63]. One of the interesting effects of this agent is the antituberculosis activity [64]. Moreover, it demonstrates good cytotoxic activity against human carcinoma cells [20,23]. Shinanolone (**4**) is the reduced product of 7-methyljuglone which was isolated from *D. kaki* L.f., *D. maingayi* Bakh., *D. morrisiana* Hance., and *D. virginiana* L. [42,65]. Shinanolone is famous for its antibacterial activity [66]. Maritinone (**5**) is the first plumbagin dimer isolated from *D. maritima* Blume., *D. kaki* L.f., and *D. samoensis* A. Gray. [43,67]. Although maritinone has significant *in vitro* cytotoxic activity ($IC_{50} = 0.06\,\mu g/ml$) [57], it was found to be inactive for *in vivo* anticancer activity evaluation [68]. Diospyrin (**6**) was first isolated from *D. montana* Roxb. in India [69]. This structure was isolated from other *Diospyros* species [5,41,42,48,63]. Diospyrin has exhibited a broad spectrum of antibacterial activity. The minimum inhibitory concentrations (MICs) range of diospyrin against *Streptococcus pyogenes* and *Streptococcus pneumoniae* was from 1.56 to 50 μg/ml, meanwhile the MICs were 25 μg/ml against *Salmonella choleraesuis* [70]. This plant-derived

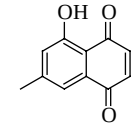
1, 4-naphthoquinone chemical structures



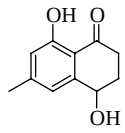
Plumbagin **(1)**



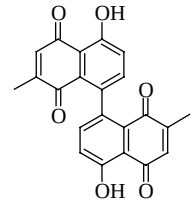
Droserone **(2)**



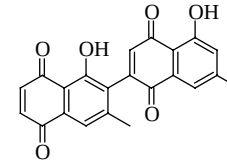
7-Methyljuglone **(3)**



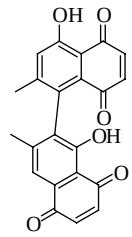
Shinanolone **(4)**



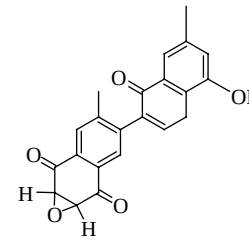
Maritinone **(5)**



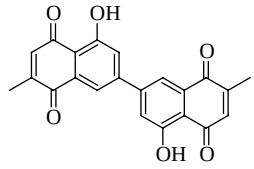
Diospyrin **(6)**



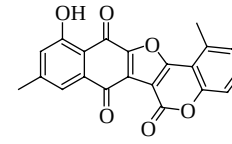
Isodiospyrin **(7)**



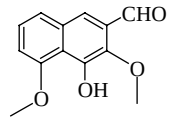
Diosquinone **(8)**



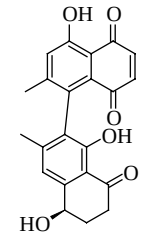
5,5'-Dihydroxy-2,2'- dimethyl-7,7'-binaphthalen-1,1',4,4'-tetraone **(9)**



Crassiflorone **(10)**



4-Hydroxy-3,5-dimethoxy-2-naphthaldehyde **(11)**



Isodiospyrol A **(12)**

Figure 1. Structures of compounds **1**–**12**.

bisnaphthoquinonoid compound illustrated *in vitro* activity against the growth of *Leishmania* [71]. It also inhibited the *in vivo* growth of Ehrlich Ascites carcinoma [72]. Isodiospyrin (**7**) has been isolated from the *D. chloroxylon* Roxb. for the first time in 1967 [73]. This unsymmetrical dimer of 7-methyljuglone was also found in the other species of *Diospyros* [74]. The Gram-positive

antibacterial activity of isodiospyrin was much more powerful than diospyrin. The antibacterial activity range for isodiospyrin was reported to be from 0.78 to 50 μg/ml [70]. Isodiospyrin showed strong *in vitro* cytotoxic activity against Hep-3B, KB, COLO-205, and HeLa cells (ED_{50} = 0.17, 1.72, 0.16, and 0.21 μg/ml) [75]. It is worth mentioning that isodiospyrin was known as a novel human DNA topoisomerase I inhibitor [76]. Diosquinone (**8**) was isolated from *D. tricolor* (Schum. & Thonn.) Hiern. for the first time [77], later it was discovered in *D. mafiensis* F. White. and *D. zombensis* (B.L. Burtt) F. White. [59,62]. It is assumed that diosquinone is the first quinone epoxide which was isolated from a higher plant [78]. Diosquinone has demonstrated a considerable antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* with MICs of 3, 15, and 16 μg/ml, respectively [79]. It was assayed for cytotoxic activity against 10 cancer cell lines and presented very good activity against all the tested cell lines with ED_{50} values ranging from 0.18 to 4.5 μg/ml [80]. In the year 2010, 5,5′-dihydroxy-2,2′-dimethyl-7,7′-binaphthalen-1,1′,4,4′-tetraone (**9**) has been isolated from *D. wallichii* King & Gamble. and manifested good cytotoxic activity against MCF-7 cell lines (IC_{50} = 0.09 μg/ml) [57]. Crassiflorone (**10**) was isolated from *D. crassiflora* Hiern. [81]. The results obtained from antibacterial investigations described that the crassiflorone might be a potential source of new antibacterial agents against tuberculosis and gonorrhea [82]. 4-Hydroxy-3,5-dimethoxy-2-naphthaldehyde (**11**) isolated from *D. assimilis* Bedd. was evaluated for its *in vitro* antiprotozoal activity against protozoan parasites belonging to the genera *Trypanosoma* and *Leishmania*. It illustrated moderate growth inhibition of the parasites, named *T. brucei*, *T. cruzi*, and *L. donovani* with IC_{50} values of 19.82, 12.28, and 38.78 μg/ml, respectively. Moreover, it displayed cytotoxic properties toward the rat skeletal myoblasts (L-6 cells) [83]. Isodiospyrol A (**12**), the isodiospyrin derivative, was isolated from *D. ehretioides* Wall. ex G. Don. It has compelling antimalarial (IC_{50} = 2.7 μg/ml) and antimycobacterial (MIC = 50 μg/ml) activities. Isodiospyrol A also had cytotoxic effect on Breast Cancer cells (IC_{50} = 12.3 μg/ml) [84].

3. Action mechanisms of the bioactive 1,4-naphthoquinones

Many 1,4-naphthoquinones isolated from *Diospyros* L. have antibacterial and cytotoxic activities; therefore, here these two bioactivities are discussed in general and in detail, respectively. Furthermore, here mechanisms of actions of the mentioned compounds are reported precisely. Two main mechanisms have been advised for the cytotoxic and anticancer characteristics of natural quinone structures [85,86]. In the first mechanism, flavin enzymes such as Cytochrome P450 reductase (NADPH) and NADH dehydrogenase convert 1,4-naphthoquinones to semiquinones through the one-electron reduction. These semiquinones can be oxidized again to quinones by transferring electrons to oxygen. This reduction and oxidation cycle is known as redox cycling. The second mechanism is related to the potent electrophilicity property of quinones which makes them able to react with thiol groups of proteins and glutathione [87]. Several studies done on plumbagin isolated from *Diospyros* L. illustrated that it can be a suitable lead compound because of having a noticeable antibacterial structure [44]. The probable responsible mechanisms of antibacterial activity can be the interaction with DNA [88] and oxidative reactions in prokaryotic cells [89]. Regarding the cytotoxic activity, redox cycling is identified as the main action mode of plumbagin [90]. In addition, many DNA manipulations can be assigned to

1,4-naphthoqunione compounds, including intercalation, alkylation, induction of strand breaks, and inhibition of DNA-related enzymes such as topoisomerases. Plumbagin also stimulates apoptosis related to reactive oxygen species mediated [91]. Crassiflorone contains the juglonyl ring so that its activity is very likely the plumbagin mechanism [83]. The cytotoxicity of juglone could also be attributed to its nucleophilic conjugation with glutathione [85]. The 7-methyljuglone antituberculosis activity might be due to the inhibition of the oxygen consumption in mycobacterium tuberculosis [92]. Diospyrin is a bisnaphthoquinonoid plant product that inhibits the growth of *L. donovani*. This effect is conducted by the inhibition of type I DNA topoisomerase activity [93]. The studies carried out on diospyrin have demonstrated anticancer activity which is carried out through the redox reactions. Two types of the redox mechanisms are commonly associated with quinones; one-electron and two-electron reductions [94–96]. The bioactivity of diospyrin is supposed to act via an one-electron reduction mechanism [97]. Isodiospyrin showed cytotoxic activity in tumor cell lines. The associated mechanism of isodiospyrin is the direct inhibition of human topoisomerase I. Likewise, isodiospyrin exhibits strong inhibitory effect on the kinase activity of human topoisomerase I with regard to ASF/SF2 (alternative splicing factor/splicing factor 2) in the absence of DNA [76].

4. Structure–activity relationships of 1,4-naphthoquinones

1,4-Naphthoquinone pharmacophore is identified to have biological effects such as anticancer and antibacterial, anti-inflammatory, antimalaria, and antileishmania [98–103]. Some small alterations in the naphthoquinones' core structures have effects on their bioactivities. For instance, existence of the oxygen or chlorine moieties on the C-3 position of the naphthoquinone nucleus leads to a complete loss of antimalarial activity [104]. *In vitro* investigations illustrated that the 2,3-disubstituted 1,4-naphthoquinones are as potent as the commonly used antifungal medicines [105]. Electron transport and respiratory pathways are crucial in growing mycobacterium species. Butyrate plumbagin was found to be the most active semi-synthesized compound against *Mycobacterium* species. Butyrate plumbagin inhibited oxygen consumption in *Mycobacterium* sp. by influencing the electron transport and respiration [106]. The obtained results from biological assays demonstrated that the ketone groups on C-1 and C-4 are important for antimycobacterial activity in 1,4-naphthoquinone nucleus. As a confirmation, the comparison between the activity of 7-methyljuglone (MIC = 0.5 μg/ml) and shinanolone (MIC = 100.0 μg/ml) can be considered. Additionally, the elimination of aromaticity between carbons 1 and 4 might also play a role in decreasing the antimycobacterium activity. The general pattern of the most active compounds such as 7-methyljuglone is very similar to the parts of the mycobacterium electron transport system like menaquinone [107,108]. On account of structural similarities between 7-methyljuglone and menaquinone, it is possible to suppose that 7-methyljuglone can interact with enzymes in the mycobacterium electron transport sequence. The redox potential difference between the 7-methyljuglone and menaquinone leads to stop the electron flow. In addition, 7-methyljuglone can prevent the adjoining of the hydrophobic side chain required in configuration of menaquinone through binding to the enzymes responsible for menaquinone production [109]. So that structural modifications of this molecule can end in generating novel potent molecules against *Mycobacterium*. The studies of structure–

activity relationships and biological activity of 1,4-naphthoquinone compounds in connection with antibacterial effects showed that the presence of a sulfur atom in 1,4-naphthoquinones leads to increase the biological activities significantly [110]. The ethanolamine derivatives of diospyrin exhibited noteworthy improvement in activity against *L. donovani* in comparison with its natural nucleus. Programmed cell death in *Leishmania* happens due to stress and drug application [111–113]. Further clarification of the molecular events linked to the apoptosis-like death induced in *Leishmania* sp. by 1,4-naphthoquinone agents like diospyrin analogs helps to recognize new targets to treat leishmanial diseases. The anticancer activity of most of novel amino derivatives of diospyrin was found to be significantly improved both *in vivo* and *in vitro*. As a result, amino derivative would act as a novel lead for the progress of valuable anticancer agents, most probably through suitable substitution in the N-acetyl moiety [114–116]. It should be noted that the introduction of an ethanolamine moiety resulted in a forceful inhibitor of the same cell line ($IC_{50} = 0.07\ \mu M$), which was nearly 50-fold more cytotoxic in comparison to its dimethyl analog ($IC_{50} = 3.18\ \mu M$) [117]. Thus, appropriate amino substitution of diospyrin followed by screening against a variety of human cell lines might lead to a good therapeutic candidate against a specific tumor strain.

5. Conclusion

This review discussed medicinally significant twelve 1,4-naphthoquinone agents isolated from *Diospyros* L. universally. We have focused on the sources, therapeutic uses, and biological activities as well as the probable mechanisms of actions. Unfortunately, most of the compounds that are claimed to show considerable activity have not been studied *in vivo*. Therefore, further *in vivo* studies of these agents are required, and a systematic investigation of these chemical-rich nucleus is needed. 1,4-Naphthoquinones are known to contain a wide array of compounds from different moieties, several of which affect specific targets in the treatment of globally important diseases. In summary, this review is presented in order to illustrate the magnitude of *Diospyros* L. as a novel bioactive source of 1,4-naphthoquinones.

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