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RESEARCH PAPER

Pharmacognostic Review on Kurdish Plant *Pterocephalus nestorianus*

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A B S T R A C T:

The genus *Pterocephalus*, one of the most important genera of Caprifoliaceae family, comprises about 30 species which are usually found in sunny, dry, rocky crevices, mostly in Europe and Western Asia. Nine species are native to the Kurdistan region of Iraq. *Pterocephalus nestorianus* Nab. is an important plant of this genera and locally known as *Lawa*. It is widely used in folkloric medicines in Kurdistan for treating inflammation and oral diseases. It is also widely used as ornamental plant and component of many herbal formulations, all around the world. The aim of the present study is to collect authentic literature on classification, geographic distribution, eco-cultural health, traditional uses, phytochemistry, biological (environmental) activities and pharmacological properties of *P. nestorianus*.

KEY WORDS: *Pterocephalus nestorianus*, Caprifoliaceae, Lawa, Phytochemistry, Pharmacology.
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INTRODUCTION :

Plant chemistry or phytochemistry has developed as a distinct discipline, someway in between natural product organic chemistry and plant biochemistry and is closely related to both (Ahamad *et al.*, 2014, 2015). It is concerned with the enormous variety of organic substances that are elaborated and accumulated by plants and deals with the understanding of the chemical structures of the secondary metabolites, their biosynthesis, turnover and metabolism, their natural distribution and their biological function in the organisms (Ahamad *et al.*, 2014). In all these researches, it is necessary to find the right methods for extraction, separation, purification and, then, identification of the many different constituents present in each plant **(**Harborne, 1998). Historically, the first new "pure" isolated compounds were strychnine (**1**) from *Strychnos* and colchicine (**3**) from Colchicum genus, followed by morphine (**4**), digitoxin (**5**), quinine (**6**) and pilocarpine (**7**), which can be considered the basis of the earliest commercial medicines, and aspirin (**8**), the first semi-synthetic drug derived from a natural remedy (Cragg and Newman, 2013). Furthermore, the accidental discovery of penicillin from the filamentous fungus *Penicillium notatum* and the findings over the therapeutic uses of penicillin G (**9**) in the first half of the last century, gave a substantial boost to the investigation of nature as the man source of novel bioactive compounds, ushering what is called the "Golden Age of Antibiotics" (Ahmadiani et al., 1998). The uses of medicinal plants are based on hundreds of years of beliefs, observations, and a rich medicinal history in Kurdistan (Alsamarkandi, 1985; Abdul and Hussain, 2018).

The genus *Pterocephalus*, one of the most important genera of Caprifoliaceae family, comprises about 30 species which are usually

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found in sunny, dry, rocky crevices, mostly in Europe and Western Asia (Iran, Turkey) (Shekha, 2007). Nine species are native to the Kurdistan region of Iraq (Shekha, 2007). These plants are widely used in folkloric medicines, all around the world, due to different biological activities such as anti-inflammatory, analgesic, antihepatotoxic, antioxidant, antibacterial, spasmolytic, hemostatic, antiseptic and astringent properties (Abdullah *et al.*, 2017). The major bioactive compounds isolated and identified from different *P. nestorianus* including hydroxycinnamic acid esters, iridoids, phenolic glycosides, monoterpenoid glucoindole alkaloids, and lignans, triterpenoid saponins, and flavonoid C-glycosides (Abdullah *et al.*, 2018). In Kurdish local medicine, *P. nestorianus* is considered to possess efficacious healing activities against various ailments; however, no systemic literature reviews available on phytochemistry and pharmacology of this plant. Folkloric medicines have become a part of eco-cultural health which directly contributes to the dynamic interaction between humans and ecosystems. This interaction provides important insights about health of the ecosystem and well-being of human populations. It is safe to say that studies related to folk medicine and medicinal plants maintain significant amount of knowledge about human and environmental health (Abdullah *et al.*, 2016). Therefore, this review paper aims to collect authentic literature on classification, geographic distribution, traditional uses, phytochemistry and pharmacological properties of *P. nestorianus*.

Figure 1. Photography of *P. nestorianus* Nab. Plant

1. METHODOLOGY

P. nestorianus, locally known with the Kurdish name of “Lawa”, is popularly employed in the herbal medicine for the treatment of oral diseases and inflammation. A complete literature survey about *P. nestorianus* was carried out by thoroughly consulting the Chemical Abstracts, Biological Abstracts, textbooks, national and international journals, herbal databases from the Internet and other published research materials, SciFinder and PubMed.

1.1. *Pterocephalus nestorianus* Nab.

The genus *Pterocephalus*, belongs to the taxonomically very complex family of Caprifoliaceae, which contains about 30 species of perennial and annual herbs and shrubs; most of them are widely distributed over the Mediterranean region and the Middle East, with about 20% in Asia and Africa (Verlaque, 1984; Fahem *et al*., 2008). Nine species are native to the Kurdistan region of Iraq (Shekha, 2007). These plants are widely used in folkloric medicines, all around the world, due to different biological activities such as anti-inflammatory, analgesic, anti-hepatotoxic, anti-oxidant, antibacterial, spasmolytic, hemostatic, antiseptic and astringent properties (Abdullah *et al.,* 2018).

1.2. Taxonomy (Hassler, 2016)

Kingdom:	Plantae
Phylum:	Tracheophyta
Class:	Magnoliopsida
Order:	Dipsacales
Family:	Caprifoliaceae
Genus:	*Pterocephalus*
Species:	*nesrorianus*

1.3. Geographic Distribution

Pterocephalus nestorianus Nab. is native throughout the world, but mainly distributed in Turkey, Iran, Iraq, as well as in Kurdistan – Iraq where, in particular, it is found in Bekher mountain, Zakho, Sharanish, Silavi Sharanish, Kani-masi, Gali-zanta, Aqra, Atrush, Lalish mountain, Duhok, Zawita, Swara-tuka, Sarsang, Gara, Matina, Sulav, Amadiya, Deralook, Rezan, Bekhma, Bradost mountain, Rowanduz, Gali Ali Beg, Shekhan, Aski-Kalak and Safeen Mountain (Shekha, 2007).

1.4. Traditional Uses

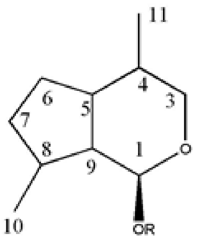
P. nestorianus is employed in the Kurdish herbal medicine for the treatment of oral diseases and inflammation. The dried aerial part powder is directly applied onto oral mucus membrane three times a day for three consecutive days. For curing inflammations, aerial parts (100 g) are left in water (1 L) for 30 min; subsequently, the infusion is filtered and drunk, 2-3 cups a day (Zhang *et al*., 2009; Abdullah *et al.*, 2017).

1.5. Phytochemical and Pharmacological Study of the Genus *Pterocephalus*

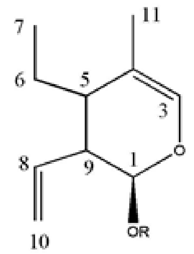
From the studies reported in the literature, it is interesting to note that many new and known compounds have been isolated from *Pterocephalus* species and their structures have been characterized by different techniques.

1.5.1 Iridoids and seco-iridoids:

Iridoids are basically a group of secondary metabolites that are present in different medicinal plants. Iridoids are monoterpenoids based on a cyclopentane-[C]-pyran skeleton (iridoid skeleton) (**10**). The name "iridoid" is derived from iridodial, which mainly consists of ten carbon atoms, though C11, and more rarely C10, is frequently missing. Oxidative cleavage at the C7, C8-bond of the cyclopentane moiety affords the so called secoiridoids (**11**).



(10)
R= H or glucose

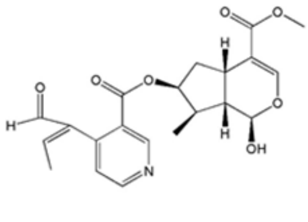


(11)
R= H or glucose

The iridoids are separated in three groups: iridoid glycosides, secoiridoid glycosides and non-glycosylated iridoids. These glycosides occur as colorless often hygroscopic powders or as colorless crystals. They are readily soluble in water and ethanol and insoluble in chloroform and ether. They are often optically active, have a bitter taste and exhibit important pharmacological actions. So far, over 2500 iridoids have been isolated from natural sources and their structures have been identified, the vast majority of them differing only for the degree and type of substitution on the basic cyclopentane ring system. However, the most distinct chemical feature among iridoids is the biosynthetic pathway occurring in the different plant groups (Damtoft *et al*., 1995).

Four new bis-iridoids, including an iridoid dimer contains a monoterpene pyridine alkaloid were isolated from the 95% aqueous ethanol extract of underground parts of *P. hookeri*. They have been called pterocenoids A-D (**12**–**15**). Their structures were elucidated by extensive spectroscopic methods, including 1D-NMR (^{1}H, ^{13}C), 2D-NMR (COSY, NOESY, HSQC and HMBC) and mass spectrometry. All these bis-iridoids were found to possess secoiridoid/iridoid subtype skeletons and inhibited TNF-induced NF-kB transcriptional activity (Wu *et al*., 2014).

Other bis-iridoids, named pterocephaline (**16**) and pterhookeroside (**17**), were reported from nature for the first time, along with the known iridoids cantleyoside (**18**) and cantleyoside methyl-hemiacetal (**19)**.



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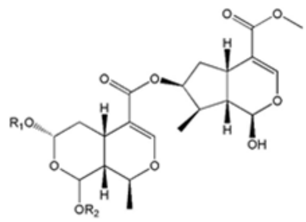
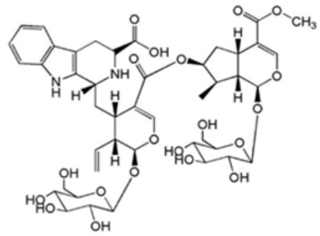


(13) $R_1 = H, R_2 = CH_3$
(14) $R_1 = CH_3, R_2 = H$
(15) $R_1 = H, R_2 = H$



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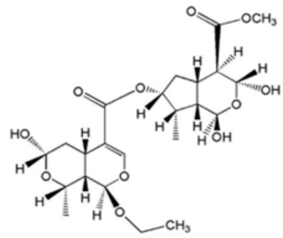

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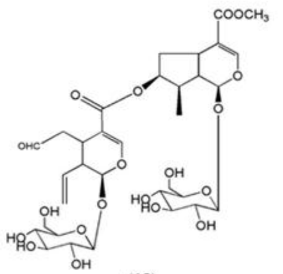

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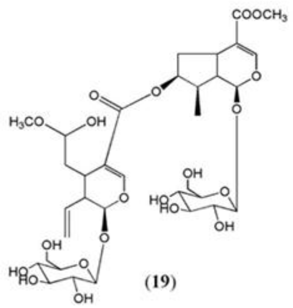
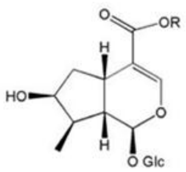
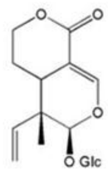


(19)

In another work, loganin (**20**), loganic acid (**21**), sweroside (**22**), isoboonein (**23**) secologanin dimethyl-acetal (**24**), secologanin (**25**), and cantleyoside dimethyl acetal (**26**) were isolated from *Pterocephalus perennis*. These compounds were found to possess high anti-hepatotoxic, antibacterial and anti-inflammatory properties (Fahem *et al*., 2008; Wu *et al*., 2014; Wu Y-C *et al*., 2014).



(20) R= CH_3
(21) R= H



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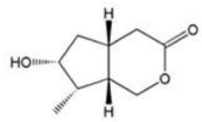

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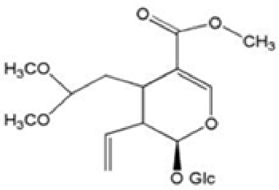

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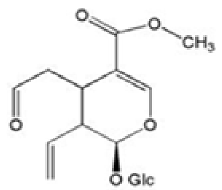

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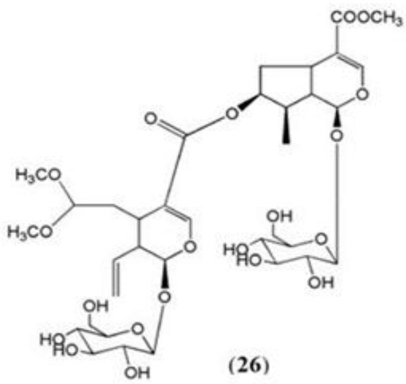

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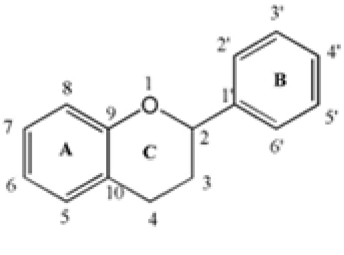
1.5.2. Flavonoids

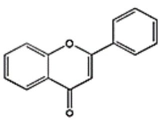
Flavonoids constitute a class of secondary metabolites that has gained great interest for the large variety and number of its members, and some remarkable biological activities. Flavonoids are relatively low molecular weight bioactive polyphenols, which play a vital role in photosynthesising cells. Flavonoids have been known for a long time to exert diverse biological effects, which include, in particular, antitumor, anti-inflammatory, antiangiogenic, antiallergic, antioxidant and antiviral properties. The structural diversity of flavonoids is the result of a number of different reactions, such as hydroxylation, methoxylation, glycosylation, methylation, and acylation.

Flavonoids are characterized by a flavan nucleus which consists of a C6-C3-C6 carbon skeleton. The basic structural feature of flavonoids is a 2-(more rarely 3-) phenyl-benzo-γ-pyrane nucleus, consisting of two phenyl rings (A and B) linked through a heterocyclic pyran ring (C), as shown in (**27**).



(27)

The various flavonoids differ in their arrangement of hydroxyl, methoxy and glycosidic side groups and in the conjunction between the A and B rings. A variation in the C ring provides a subdivision in different classes. Thus, according to their molecular structure, they are divided into these classes: flavones (**28**), flavonols (**29**), isoflavones (**30**), flavanones (**31**), dihydroflavonols (**32**), anthocyanidins (**33**), catechins (**34**), chalcones (**35**) neoflavonoids (**36**).



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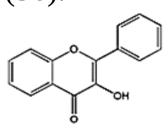

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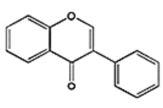

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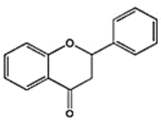

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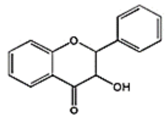

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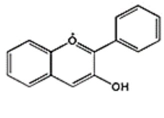

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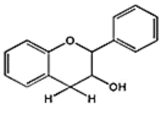

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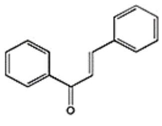

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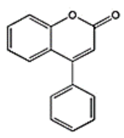
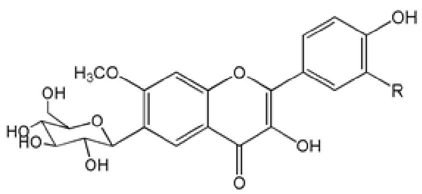


(36)

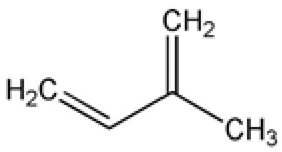
In the past decade, only two flavonoid C-glycosides were isolated from *sanctus*, identified as luteolin-6-*C*-β-D-glucoside-7-*O*-methyl ether (**37**) and apigenin-6-*C*-β-D-glucoside-7-*O*-methyl ether (**38**) on the basis of spectroscopic studies (Fahem and Abdelaaty, 2006).



(**37**) R= OH
(**38**) R= H

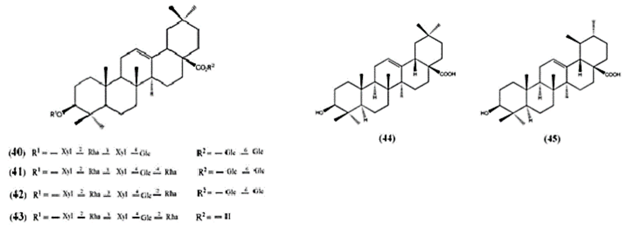
1.5.3. Terpenoids

Terpenoids are a large range of secondary metabolites widely distributed in nature. All terpenoids are formally based on the isoprene unit (**39**) and their carbon skeletons are build up from the union of two or more of these C_5 units. They comprise such different substances as the volatile mono-and sesquiterpene (C_{10} and C_{15}) components of the essential oils, the less volatile diterpenes (C_{20}), and the non-volatile triterpenoids (C_{30}) and derived steroids, as well as the carotenoid pigments (C_{40}) (Fahem and Abdelaaty, 2006; Harbone, 1998).



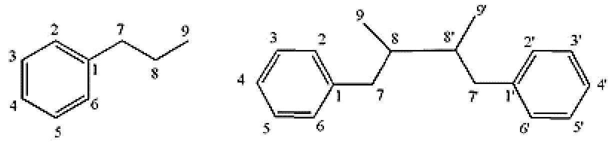
(**39**)

According to the reported literature (Jun *et al*., 1993; Yang *et al*., 2007), four novel triterpenoid saponins, named hookeroside A (**40**), hookeroside B (**41**) hookeroside C (**42**), and hookeroside D (**43**), together with two common bioactive triterpenoids, oleanolic acid (**44**) and its isomer ursolic acid (**45**), were isolated from *P. hookeri* by capillary zone electrophoresis and other chromatographic techniques. The structures were determined on the basis of chemical and spectral evidences. Triterpenoid saponins have drawn the attention of researchers because of their diverse bioactivities, including anti-inflammatory, anti-cancer, anti-microbial effects. Due to their significant pharmacological activities, plants rich in triterpenoid saponins are usually exploited as drug sources.



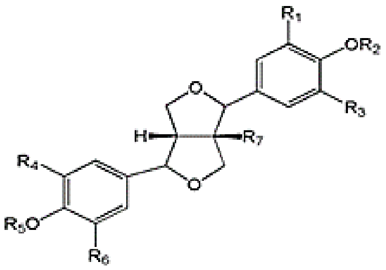
1.5.4. Lignans

Lignans form a rather large class of secondary metabolites synthesized by plants exhibiting a wide spectrum of important biological activities. In fact, hepatoprotective, anti-inflammatory, antiviral, antimicrobial, anticancer, cancer prevention and antioxidant effects are the main biological properties attributed to lignans in literature (Toshiaki, 2003). The "lignan" a group of dimeric phenylpropanoids with the basic skeleton **47**, in which two C_6-C_3 phenylpropanoid units (**46**) are attached by their central carbon C_8.



(**46**) (**47**)

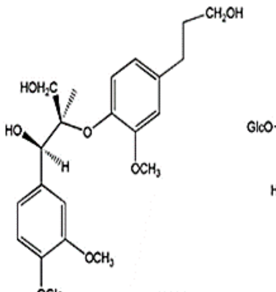
Previous phytochemical investigations on *Pterocephalus* species led to the isolation and identification of several lignans, including (+)-1hydroxypinoresinol 4''-*O*-β-D-gluco-pyranoside (**48**), (+)-1-hydroxypinoresinol 4'-*O*-β-D-glucopyranoside (**49**), (+)-*s*yrin-garesinol 4"-*O*-β-D-glucoside (**50**), (7*R*, 8*S*)-*erythro*-7,9,9'-trihydroxy-3,3'-dimethoxy-8-*O*-4'-neolignan 4'-*O*-β-D-glucoside (**51**), cedrusin 4'-*O*-β-D-glucoside (**52**), urolig-noside hexaacetate (**53**), *trans*-lariciresinol 4-*O*-β-D-glucoside hexaacetate (**54**) (Graikou *et al*., 2006; Wu *et al*., 2014).



(48) $R_1=R_2=R_4=H$ $R_3=R_6=OCH_3$ $R_5=Glc$ $R_7=OH$

(49) $R_1=R_4=R_5=H$ $R_3=R_6=OCH_3$ $R_2=Glc$ $R_7=OH$

(50) $R_1=R_3=R_4=R_6=OCH_3$ $R_5=Glc$ $R_2=R_7=H$



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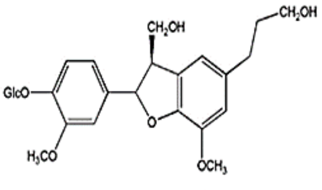

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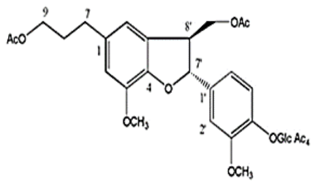

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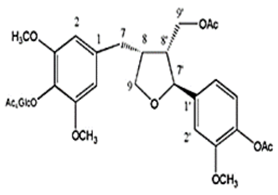

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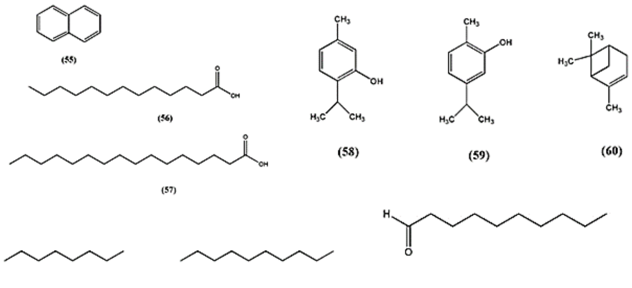
1.5.5. Essential oils

Essential oils contain hundreds of highly volatile components, including terpenoids, aldehydes, esters, carboxylic acids, ketones and alcohols. These mixtures are extracted from leaves, flowers, bark, roots or other parts of the plant. The odour and taste of an essential oil are mainly determined by the oxygenated constituents; moreover, the fact that they contain oxygen atoms gives them some solubility in water and considerable solubility in alcohol.

The composition of the essential oils from the aerial parts of *P. canus* and *P. gedrosiacus* (Hooshang *et al*., 2011; Akhgar and Safavinia 2016), which grow in the wild in Iran, have been previously reported. The main constituents of the *P. canus* oil were naphthalene (42.4%) (**55**), tridecanoic acid (7.9%) (**56**), and palmitic acid (7.9%) (**57**), where's the characteristic components of the *P. gedrosiacus* oil were thymol (31.6%) (**58**), carvacrol (7.7%) (**59**), α-pinene (3.3%) (**60**), *n*-octane (15.2%) (**61**), *n*-decane (3.8%) (**62**), and *n*-decanal (4.4%) (**63**).



(55) (56) (57) (58) (59) (60) (61) (62) (63)

It has become more evident in studies that degradation of an ecosystem negatively influences human health; thus, that human health is linked to ecological context holds an important place in ecosystem services. The benefits of ecosystem services for people can be both material and quantifiable; for instance, while climate regulation and food supply is considered as material advantages, aesthetic and recreation is considered as quantifiable advantages.

2. CONCLUSIONS

In recent years, phytochemical investigation of herbal flora has received much attention of the scientists and pharmaceutical industries so as to know about novel herbal compounds which can be screened for their therapeutic potential to treat several health disorders without side effects. This genus could be a promising source for the development of novel strategies to cure fatal maladies. Further consideration, standardization and clinical trials of pharmacological potential of *P. nestorianus* is essential for its recommendation as a medicine at safer level. The information summarized above will serve as a reference tool for the research groups working in the area of developing alternatives of synthetic drug. However, there is a need to evaluate the therapeutic potential on modern scientific lines through clinical trials, phytochemicals and pharmacological studies. In addition, this study has showed that conducting studies on medicinal plants help people not only establish a relationship with the environment but also collect important knowledge about their possible contributions to human health.

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