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REVIEW ARTICLE OPEN ACCESS

Review on *Darunaj-aqrabi (Doronicum hookeri C.B. Clarke)*: an Unexplored Medicinal Plant of Unani System of Medicine

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Abstract

Darunaj-aqrabi (*Doronicum hookeri* CB Clarke ex. Hook.f.) is a medicinal plant (Asteraceae) that has long been used in the Unani Medicine System (USM) to produce cardiac tonic (rejuvenating and stimulant), nerve tonic, carminative, embryo protective, antidote, etc. functions in various formulations. It is extremely valuable for palpitations, so it is included in medicines specific to the heart. Due to their anti-inflammatory and protective properties (repair), rhizomes are widely utilised in compound formulations that have a tonic effect on the body. The main objective of this review is to show the significance of *Darunaj-aqrabi* in USM. This review provides important information focusing on traditional practice, phytochemistry, and the medical profile, thus identifying areas for research and future opportunities for research and development of this plant. All available information associated with *Darunaj-Aqrabi* in internationally recognised science repositories, including PubMed, Direct Science, Scopus, SciFinder, Google Scholar, Microsoft Academy, and Web Science, is searched. Additional information was collected in an old USM document on herbs, Unani Pharmacopoeia, and so on. These texts support its traditional use in formularies or by local people, such as digestion, carminative, child protection, cardiotonic, stomach tonic, liver tonic, lithotriptic, antidote, etc. The main phytochemical elements are alkaloids, saponins, flavonoids, photoactive thiophenes, sesquiterpene alcohol, paralianchol, and its acetophenone. There is limited information available on this plant. The review studies support its use as a digestive, carminative, child protection, cardiotonic, stomach tonic, liver tonic, lithotriptic, antidote, etc. However, many features of this tool are still unknown. In line with this, there's insufficient detail in phytochemistry and a toxic profile. Thanks to the widespread use of *Darunaj-aqrabi*, further research into its pharmaceutical activities, phytochemistry, toxicity, and side effects is required to work out its therapeutic value.

KEY WORDS: darunaj-aqrabi, darawnay, antibacterial, antifungal, antioxidant and hepatoprotective etc.

1. INTRODUCTION

USM (also known as Greco-Arab medicine) is an ancient system of medicines based on the concept of the Humoral Theory of Hippocrates (460–377 BC). It is most commonly practiced in the Indian subcontinent and has a concept and ancient principles of disease management. The drugs used in this system are of natural origin, like plants, minerals, and animals[1]. Herbal remedies have historically been the source of almost all drugs. The medicinal use of herbs is primarily derived from popular knowledge approaches that assess their beneficial value in the treatment and prevention of various diseases. In this way, traditional medicine has been of considerable importance to science and has made an important contribution to the discovery of new substances and the selection of species for research[2].

The Asteraceae family deserves special attention among the other plant families studied. This family is made up of approximately 1,500 genera and 25,000 species worldwide[3], including the genus Doronicum, which includes 26 species and 4 subspecies present in Asia, Europe, and North Africa[4].

According to the Unani literature, "*Doronicum hookeri*" is one of the most commonly used drugs in USM. It is a popular medicinal plant of the family Asteraceae. It is distributed between 12,000 and 14,000 feet in the Himalayas at Lachen and Tungu, Sikkim, Nepal, Bhutan, and Tibet[5, 6]. Rhizomes of *Doronicum falconeri* Hook. f. (native to the North Western Himalayas), *Doronicum roylei* DC. (native to Punjab), and the European species (*Doronicum pardalianches* Linn. and *Doronicum scorpioides*) are introduced into India and are also classified as *Darunaj-aqrabi*[6,7]. It is said that this ancient drug was originally from Greece and Syria[8].

The term Doronicum is derived from the Arabic word "Darawnay," used by at least two distinct species[4]. However, some researchers have reported that Doronicum

is a direct transliteration of the Arabic word "Doronigi," an original contribution to Islamic drugs[9]. Pre-Linnaean botanists (Dioscorides, 1554, 1557; Dodoens, 1574) and other Greek writers referred to the species Doronicum as *Aconitam pardalianches*, and Ibn Sina (known in the West as Avicenna, c. 980–1037) probably introduced the plant into western culture[4]. The rhizomes of *Doronicum hookeri* are traditionally used as a constituent of cardiac and nervine tonics, are exhilarant, act as a stomachic, and dissolve trapped gases. *Doronicum pardalianches* Linn. are used in nervous depression, melancholia, and as a constituent of cardiac tonic preparations, and the rhizome of *Doronicum roylei* DC is reported to prevent giddiness caused during high attitude ascents[6]. The rhizomes of *Darunaj-aqrabi* are unique; they look like the tail of a scorpion and are white like alabaster. This produces inulin instead of starch. It is bitter and acrid in taste and known to be toxic in Persia. It is useful in nervous depression and is prescribed for scorpions and insect bites[10]. This drug is also mentioned in Kitab al-Adwiyah al-Qalbiyah by Ibn Sina and is quite effective in the treatment of cardiac diseases[11].

Table 1: Vernacular Names of *Darunaj-aqrabi* (*Doronicum hookeri* CB Clarke ex. Hook.f.)

Sanskrit	Vrishichka
Hindi	Tarang
English	Leopard's Bane
Arabic	*Darunaj-aqrabi*
Persian	Darunak
Urdu	*Darunaj aqrabi*

Table 2: Taxonomical Classification of *Darunaj-aqrabi* (*Doronicum hookeri* CB Clarke ex. Hook.f.)

Botanical name: *Doronicum hookeri*	
Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Asteridae
Order	Asterales
Family	Asteraceae
Genus	Doronicum
Species	hookeri

It has been shown to have antibacterial, antifungal[12], hepatoprotective, and antioxidant activity[13,14]. This article aimed to review the traditional uses of *Darunaj aqrabi* in the USM as well as its botanical, phytochemical, and pharmacological activities. The common name and taxonomic classification are mentioned below.

2. METHODS

The literature of *Doronicum hookeri* was obtained from online databases including PubMed, Google Scholar, Web of Science, and Science Direct, and a library search was also conducted on classical Unani books, PhD theses, and published and unpublished books. The keywords used for the search was *Doronicum hookeri*, *Nannoglottis hookeri*, *Doronicum scorpioide*, *Doronicum*, *Darunaj-aqrabi*, *Daroonaj-aqrabi*, *Darunaj*, *Daroonaj*, and Leopard's Bane. For Arabic writings, the term (بِ قربی درونج) was used. Scientific names and synonyms were validated through the plant list (www.theplantlist.org).

3. BOTANICAL DESCRIPTION

3.1 Habitat

It is distributed in the Sikkim Himalayas between 12,000 and 14,000 feet. Also found in Syria, Africa, Iran, Europe, and Spain[15,6,7].

3.2 Morphology

A robust herb, 0.3–0.6 m high. Radical leaves 0, or soon withering; cauline 10-15 by 2.5–5 cm, often unequal-sided. Leaves are all narrowed into short, ½- amplexicaul petioles, oblong or elliptic lanceolate, obtuse or acute, entire or irregularly toothed. Heads 1-2, 6.3 cm. glandular-pubescent. Involucral bracts, ovate-lanceolate, acuminate. Achenes is all purpose. Pappus is short and reddish[6].

3.3 Microscopic Structure

The transverse section of the rhizome shows epidermis, cortex, and vascular tissue; epidermis uniseriate, made up of brick-shaped cells, replaced at several places by sclerenchymatous hypodermis; hypodermis tri to five seriate, sclerenchymatous cells filled with brown pigment; cortex multiseriate, parenchymatous with intercellular spaces; some of the cells filled with brown pigment; cortex also contains cells with inulin crystals and aggregations of calcium oxalate crystals; groups of sclereids are also scattered in the cortex; lysogenous cavities filled with oil are seen in the cortical region; vasculature contains a peripheral ring of pericycle made of sclerenchyma; vascular bundles: conjoint, collateral, open, and endarch; xylem contains vessels with reticulate and scalariform thickenings; pith is crushed, leaving large spaces in the centre[23,24].

3.4 Description of *Darunaj-aqrabi* in Unani literature

Darunaj-aqrabi is one of the important plant-derived drugs widely used in different dosage forms of Unani medicines. It is the dried rhizomes of Doronicum hookeri[6]. (Figure 1). The rhizomes are looking like the tail of a scorpion, so-called Aqrabi (the morphology of the rhizome is similar to the scorpion's tail), taken from the Arabic word 'Aqrab' used for scorpion fibrous, nodular, hard, and heaving weight. The colour of the outer surface of the rhizome is brown or greyish, whereas it is white from inside. It is as thick as a finger; in taste, it is starchy, astringent, bitter, and acidic. It has a characteristic odour. According to Unani classical textbooks, there are two variants of *Darunaj-aqrabi*: Roman and Persian. The rhizomes of the Roman variety are of high quality, especially those that are very bitter, hard, and white inside[16,25].

Figure 1: Flower of *Doronicum hookeri*

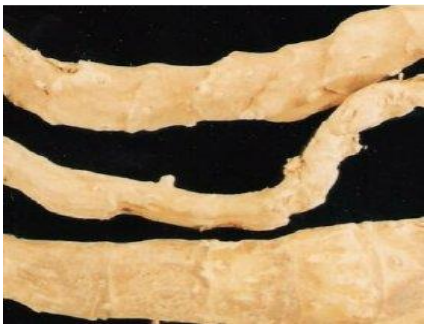

Figure *2:* *D. hookeri* Hook. f. roots

Figure 3: Dried rhizomes of *Doronicum hookeri* (Source: Drug Museum of National Institute of Unani medicine)

3.5 Properties of Darunaj-Aqrabi in Unani medicine

3.5.1 Temperament

Mizaj (temperament) is one of the principal fundamental concepts of USM, and most of the drug's act on their temperament. The drug's mizaj is expressed in terms of four kaifiyat (qualities), i.e., har (hot), barid (cold), yabis (dry), and ratab (moist)[26,27]. The temperament of *Darunaj-aqrabi* has been described as hot and dry in the third degree[15,16,28-30].

3.5.2 Pharmacological Action

It possesses Muhallil (resolvent), Mulattif (demulcent), Musakhkhin (calorific), Mufarreh Qalb (exhilerant), Muqawwi-ī-qalb (cardiotonic), Hāzim (digestive), Kāsir-ī-reyāh (carminative), Muqawwi-ī-mi'da (stomach tonic), Muqawwi-ī-jigar (liver tonic), Mufattit sang gurda wa mathana (lithotriptic), Muhafiz-ī-janin (protective of the foetus), Dafe-e-fawaq, and Tiryaq samum (antidote) properties[15,28–32].

3.5.3 Therapeutic Uses

It is used in the treatment of Zo'f-ī-Qalb (weakness of the heart), Khafqān Bārid (palpitation due to cold), Tā'un (plague), Fālij (hemiplegia), Laqwā (Bell's palsy), Melancholia (depression), Nafakh-ī-Shikam (flatulence), Waja al-Mi'da (abdominal pain), Dard Rahim Rehi (uterine pain due to accumulation of gases), Uterine flatulence, Insomnia, Riyah al-Afrisa (displacement of vertebral column), Awram Batina (superficial inflammation), and snake and scorpion bite[16, 28, 29, 31, 32]. Eating it along with figs is effective against all kinds of poisons, including snake and scorpion bites[29,31]. It attenuates (talteef) and dissolves (tahleel) intestinal inflammation[32]. Using it with sugar is beneficial for phlegmatic headaches and chest pain[16]. It strengthens the heart and proves to be useful in palpitation[29]. Due to its antidote properties, it is being used in epidemic diseases, especially plague[33].

3.5.4 Adverse Effect

Darunaj-aqrabi causes headaches and is particularly harmful to people with a hot temperament[16,30].

3.5.5 Correctives/Corrigent

Along with having important pharmacological activity, some of the drugs in Unani medicines may also produce toxic effects because of their inherent nature. Hence, to optimise the therapeutic effect of drugs, they are subject to certain corrective measures (Islah-e-Advia), as described in Unani literature. This is done to reduce the toxicity of drugs by partially modifying them through specific corrective procedures (Amal-e-Tadbeer). If the application of corrective measures to the drug is not possible, then another drug that serves as a corrective agent (Musleh) is either admixed or used accordingly with the first drug to minimise its unwanted effects[34]. To reduce the harmful effects of *Darunaj-aqrabi*, Bādiyan (*Foeniculum vulgare* Mill.), Nashāshtā (carbohydrates), Sharbat-e-seb (apple juice), Rubb-e-Angoor (dry extract of grape), and Rebaas are used as correctives[28–30].

3.5.6 Substitute

A substitute (Badal) is used when the original drug is not available. No drug can be a complete substitute for another drug. If a drug is substituted by some other drug having the same property, the second drug should be a substitute for the original drug for that very specific activity[1,35]. Al-Razi (865–925 AD) has accounted that "in case the drugs required for the treatment of a particular disease are not available and the physician is unaware of their substitutes, which may be used in place of the required drugs, the objectivity and benefit of this medical system would cease," as all crude drugs cannot be arranged all the time at every clinical unit[34]. In heart diseases, a substitute for *Darunaj-aqrabi* is an equal dose of Zarambād (*Curcuma zedoaria*) and 1/3rd dose of Qarnful (*Syzygium aromaticum*)[16], and for uterine flatulence, an equal dose of Zarambād (*Curcuma zedoaria*) and 2/3rd dose of Qarnful (*Syzygium aromaticum*) is given. According to some scholars's substitutes for *Darunaj-Aqrabi*, they are Suranjan (*Colchicum luteum*), Aqer Qerha (*Anacyclus pyrethrum* DC.), and Qust (*Saussurea lappa*)[28,29,31,36].

3.5.7 Dose

It is given in a dose of 3.5-7 g[16].

3.6 Compound Formulations

There are different dosage forms of Unani medicines that contain *Darunaj-aqrabi* as one of the ingredients, such as Dawa al-misk, Laboob Kabir Khas, Mājun Hamal Ambari Alvi Khān, Mufarreh Yaquti, Mājun-e-Alkula, Khamira Marwareed Banuskha-e-Kalan, Khamira Murakkab, Mājun Chob Chini Ba Nuskha Kalan, Mājun Murawweh ul Arwah, Mufarreh Azam, Arq Ambar, Habb-e-Muqawwi Khas, Nawed-e-Nau, Shababi, Ambari, Qalbeen, Yashbi, Jawarish Muqawwi- ī-mi'da[16,29,37,38]. Brief descriptions of compound formulations mentioned in different Qarabadeen are given in Table 3.

Table 3: Compound formulations containing *Darunaj-aqrabi* and their indications

S.no.	Formulations	Pharmacological actions	Therapeutic Use	Dose	Reference
1.	*Dawa ul-misk moatadil*	*Muqawwi-ī-Aam* (General tonic), *Muqawwi-ī-qalb* (cardiotonic)	*Zo'f-ī-Aza-ī-Raeesa* (Vital organs insufficiency), *Khafqān* (palpitation), *Malikhuliya* (Melancholia), *Waswas* (Psychosis)	5 to 10 g with water at bedtime	[39,40]
2.	*Dawa ul-misk Har sada*	*Muqawwi-ī-qalb* (cardiotonic), *Muqawwi-ī-dimāg* (neuro tonic)	*Khafqān (palpitation), Malikhuliya (Melancholia), Waswas (Psychosis), Amrāz-ī-balghamiyā wa sawdaviā (diseases which occur due to excess of phlegm and black bile), Mirghi (epilepsy), laqwa (Facial palsy)*	5 g with 84 ml of Arq Badyaan in morning	[39,40]
3.	*Dawa ul-misk Har jawahar wala*	*Muqawwi-ī-qalb* (cardiotonic), *Muqawwi-ī-dimāg* (neuro tonic)	*Khafqān* (palpitation), *Malikhuliya* (Melancholia), *Waswas* (Psychosis), *Amrāz-ī-balghamiyā wa sawdaviā* (diseases which occur due to excess of phlegm and black bile)	5 g with 84 ml of Arq Badyaan in morning	[39]
4.	*Dawa ul-misk moatadil jawahar wala*	*Muqawwi-ī-qalb* (cardiotonic), *Muqawwi-ī-jigar* (liver tonic), *Muqawwi-ī-mi'da* (stomachic)	*Khafqān Sawdāwī* (Melancholic palpitation), *Mālankhūliya Marāqī* (Psychoneurosis), *Zo'f-ī-Qalb* (Weakness of Heart)	3-7 g with 60ml of Arq Badyaan	[39]
5.	*Dawa ul-misk*	*Muqawwi-ī-Azae Raesa* (Tonic forPrincipal organs)	*Malikhuliya* (Melancholia), *Waswas* (Psychosis), Fālij (Hemiplegia), laqwa (Facial palsy)	5 g with 125 ml of Arq ghaozaban	[41]
6.	*Laboob Kabir Khas*	*Muqawwi-ī-bāh* (aphrodisiac), *Muqawwi-ī-dimāg* (neuro tonic), *Muqawwi-ī-a'sab* (nervine tonic), *Muqawwi-ī-qalb* (cardiotonic) and *Muqawwi-ī-gurda* (renal tonic)	*Zo'f-ī-bāh* (sexual weakness), *Zo'f-ī-*dimagh, *Zo'fī-a'sab* (nervine weakness)	5 g with milk or water before breakfast	[39]
7.	*Mājun Hamal Ambari Alvi Khān*	*Muhafiz-ī-janin* (protective of foetus)	Useful in threatened miscarriages, excess bleeding after delivery or for women whose offspring's die at birth	5 g with milk before breakfast	[41,42]
8.	*Mufarreh Yaquti*	*Mufarreh qalb* (exhilarant), *Muqawwi- ī-Azae Raesa* (Tonic for Principal organs), *Mushtahī* (appetizer)	*Nāf-ī Is-hal* (antidiarrheal), *Nāf-ī-*Amrāz-i-Rehem (Beneficial in Uterine Diseases), *Amrāz-ī-Qalb* (cardiac diseases)	5 g with 250ml of milk in morning	[43]
9.	*Mājun-e-Alkula*	*Muqawwi-ī-gurda* (renal tonic) wa Mathāna, *Muqawwi-ī-bāh* (aphrodisiac), *Muqawwi-ī-a'sab* (nervine tonic)	Amrāz-i-gurda (Disease of kidney), Amrāz-i-mathana (Disease of bladder), *Zo'f-ī-*Kulya (weakness of kidney), *Zo'f-ī-*Masana (weakness of bladder), *Zo'f-ī-bāh* (sexual weakness)	6 g twice a day	[42,44]
10.	*Khamira Marwareed*	*Muqawwi-ī-Azae Raesa* (Tonic for Principal organs), *Muqawwi-ī-qalb* (cardiotonic), *Muqawwi-ī-dimāg* (neuro tonic)	*Khafqān* (palpitation), *Zo'f-ī-Qalb* (Weakness of Heart), *Amrāz-i-qalb* (disease of the heart)	4.5 g twice a day	[45]
11.	*Khamira Marwareed Banuskha-e-Kalan*	*Muqawwi-ī-qalb* (cardiotonic), *Muqawwi-ī-dimāg* (neuro tonic) and *Muqawwi-ī-Hafiza* (Memory tonic)	It is beneficial in *Khafqān* (palpitation), Moti Jhhara, Chechakand Debility after disease.	3-5 g with 125ml of Arq Gaozaban twice a day	[43]
12.	*Khamira Murakkab*	*Muqawwi-ī-qalb* (cardiotonic)	Amrāz-i-qalb (disease of the heart), *Zo'f-ī-Qalb* (Weakness of Heart), *Khafqān* (palpitation), Amrāz-i-dimagh (disease of brain)	5 g with milk before breakfast	[41]
13.	*Khamira-e-Abresham sada*	*Muqawwi-ī-qalb* (cardiotonic), *Muqawwi-ī-dimāg* (neuro tonic)	*Khafqān* (palpitation), Karb (Distress), *Zo'f-ī-Qalb* (Weakness of Heart)	5-10 g. with water twice a day after meal.	[24]

14.	***Safoof darunaj***	***Muqawwi-ī-qalb* (cardiotonic)**	***Khafqān Bārid* (palpitation due to cold), *Zo'f-ī-Qalb* (Weakness of Heart)**	**4.5 g with honey**	**[45]**
15.	*Mājun Murawweh ulArwah*	*Muqawwi-ī-qalb* (cardiotonic), *Muqawwi-ī-dimāg* (neuro tonic), *Muqawwi-ī*-Jiger (Liver tonic),*Muqawwi-ī-mi'da* (stomachic), *Muqawwi-ī-Hafiza* (Memory tonic), *Muna-ash Hararat Ghareezi* (Procurator of Latent Energy of Body)	*Zo'f-ī-Qalb* (Weakness of Heart), Amrāz-i-jigar (disease of liver), *Khafqān* (palpitation),	1g twice a day	[42]
16.	*Mufarreh Azam*	*Mufarreh qalb* (exhilarant), Dafe Khafqan (Relieves palpitation), *Muqawwi-ī-bāh* (aphrodisiac), Nafe Heza (Beneficial in Cholera), Nafe Taoon (Beneficial in Plague).	*Khafqān* (palpitation), Heza (Cholera), Taoon (Plague), *Zo'f-ī-bāh* (sexual weakness)	5 g with water in the morning	[41]
17.	*Arq Ambar*	*Muqawwi-ī-Aam* (General tonic)	*Zo'f-ī-Qalb* (Weakness of Heart), Zof- e-Dimagh (Weakness of the brain), Zof-ī-Jigar (Weakness of the liver), Ghashi (Fainting), Naqahat (Asthenia)	60 ml, taken orally along with Sharbat- e-Anar.	[23]
18.	*Yaquti*	*Muqawwi-ī-qalb* (cardiotonic)	*Khafqān* (palpitation), Sadr-o-Duwār (vertigo), *Zo'f-ī-Qalb* (Weakness of Heart)	4.5 g with water in the morning	[45]
19.	*Yaquti har*	*Muqawwi-ī-qalb* (cardiotonic), *Muqawwi-ī-dimāg* (neuro tonic), *Muqawwi-ī-gurda* (renal tonic)	Amrāz-i-qalb (disease of the heart), *Khafqān* (palpitation), carminative	1.75-3.5 g with water in the morning	[45]
20.	*Majun isteqrarehamal*	Isteqrare hamal (to promote conception)		1 g with water in the morning	[45]
21.	*Majoon hakim alvi khan*	Antiepileptic	*Ummus subiyan* (infantile Epilepsy)	4.5 g twice a day	[45]
22.	*Hab-e-Ta'un*	To prevent *Ta'un* (Plague)	Beneficial in plague	1 or 2 pills three times with arq bedmushk or arq ghulab	[39,42]
23.	*Hab-e-Amber Momiyaie*	*Muqawwi-ī-Aam* (General tonic), *Muqawwi-ī-bāh* (aphrodisiac), *Muqawwi-ī-qalb* (cardiotonic)	*Zo'f-ī-bāh* (sexual weakness), *aryān* (spermatorrhoea), *Ehtelām* (nocturnal emission), *Surat-ī-inzāl* (premature ejaculation), Strengthens Vital organs, Removes sexual debility and impotency, Enhancement of normalsexual function	2 pills with cow milk atbedtime	[42]
24.	Mufarreh Shaikhul-Rais	*Mufarreh qalb* (exhilarant), *Muqawwi-ī-qalb* (cardiotonic), Muqavvi Aaza Raisa (Vital organ tonic)	Huma Diq (Tubercular fever), Huma Saudavi (Melancholic fever) and *Khafqān* (palpitation),	3 g with water in the morning	[46]
25.	Mufarreh motadil	*Muqawwi-ī-qalb* (cardiotonic), *Mufarreh qalb* (exhilarant)	Amrāz-i-Qalb (disease of the heart), *Zo'f-ī-Qalb* (Weakness of Heart)	6 g with water in the morning	[40]
26.	Mufarreh har	*Mufarreh qalb* (exhilarant), Dafe Khafqan (Relieves Palpitation), *Muqawwi-ī-qalb* (cardiotonic)	Amrāz-i-Qalb (disease of the heart)	9-12 g with water in themorning	[40]

3.7 Shelf Life

Ancient Unani physicians evaluated drug shelf-life by organoleptic drug characters, i.e., Zahiri sifat (external characteristics), rang (colour), boo (smell), maza (taste), qiwam (consistency), saakht (structure), wazan (weight), safai (clarity), jila (cleanliness), and tazgi (freshness). When all these characteristics of the drug are safe, it is considered that the drug is stable and its shelf life is maintained, and if any changes are observed, accordingly, it is considered that it has lost its shelf life. The shelf life of *Darunaj-aqrabi* is approximately 10 years[47,48].

3.8 Bio-Active Compounds

Doronicum hookeri's chemical constituents have not yet been studied and described. Recently, a new allelochemical (Figure 3; compound 1) 5, 7,4'-trihydroxy-6-methoxy-flavone-5-O-α-L-rhamno-pyranosyl-1→4)-O-α-L-arabinopy-ranosyl-4'-O-β-D-glucopyranoside, along with two known compounds (Figure 4; compound 2). 5-hydroxy-3, 7, 4'-trimethoxyflavone and (Figure 5; compound 3) 7, 3'-dihydroxy-5, 4', 5'-trimethoxy isoflavone have been isolated from the methanolic extract of the flowers of *Doronicum hookeri*[49]. Syed *et al.*[13] isolated flavonoids, alkaloids,

saponins, and cardiac glycosides from the rhizomes. Phenolic contents were isolated by Gupta *et al.[*14]. Alkaloid otosenine is believed to have cardiovascular properties[50].

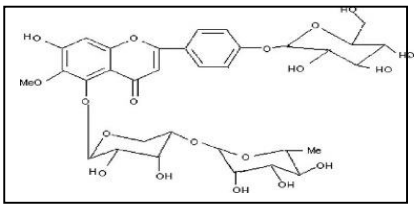

Figure 3: Compound 1

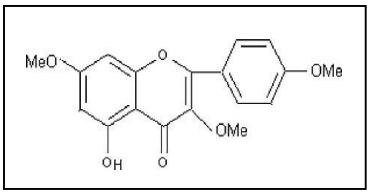

Figure 4: Compound 2

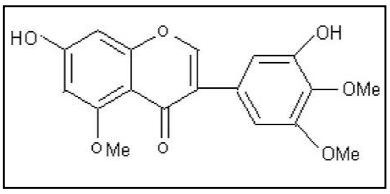

Figure 5*:* Compound 3

3.9 Pharmacological Studies

Doronicum hookeri has been reported for its antifungal[51], antimicrobial activity[12], antioxidant[14], and hepatoprotective activities[13]. Recently, cardioprotective, antiatherogenic, and reducing effects of blood pressure have been shown[5].

The effect of *Doronicum hookeri* has not been evaluated, but a variety of compound formulations containing it have been tested clinically. Sultana *et al.* [52] identified the fertility-enhancing effect of Habb-e-Hamal containing *Doronicum hookeri* as one of its components. In another study, *Safoof Darunaj* was administered in powder form at a dosage of 5 g twice daily along with 200 ml of Ma'ul Asl (Honey Water) for 30 days. The study showed that the test drug has a significant effect on improving cough, breathlessness, pulmonary rales, and oedema of the extremities[53]. Similarly, Qalbeen (2 pills twice a day), an herbomineral formulation containing *Doronicum hookeri*, was found to relieve chest pain, dyspnea, and palpitations in patients with ischaemic heart disease after 90 days of treatment [50]. Khamira Marwareed, an herbo-mineral Unani preparation containing *Darunaj-aqrabi* as one of its ingredients, is an effective and potent cardiac tonic with well-known antioxidant properties[54].

3.10 Antifungal Activity

Bioactive chemicals obtained from natural sources such as plants may be a potential source of antifungal agents, particularly in the present situation where resistance to antifungal agents has been adopted by human and plant-parasitic pathogens [55]. *Doronicum hookeri* has shown promising *in-vitro* antifungal activity. Dichloromethane and methanol extracts of *Doronicum hookeri* rhizome were evaluated against *Saccharomyces cerevisiae* and *Candida albicans* at concentrations of 1000 and 500 µg/ml in the nutrient agar medium, which demonstrated potent antifungal activity[12].

3.11 Antibacterial activity

In an *in-vitro* study, *Streptococcus faecalis* was cultivated in nutrient agar media with the addition of a mixture of dichloromethane and methanol (1:1, v/v) extracts of *Doronicum hookeri* in different concentrations. The growth of the bacteria is inhibited at 500 µg/mL concentrations of the extract, showing its antibacterial activity[12]. *Streptococcus faecalis*, also known as *Enterococcus faecalis*, is the main pathogen of the genus Enterococcus, which causes around 95% of enterococcal infections, including infections of the urinary tract, infections of the biliary tract, ulcers (e.g., bed sores), wounds (especially abdominal), and occasionally endocarditis or meningitis. It is a normal vaginal commensal and intestinal tract[56].

3.12 Antioxidant activity

3.12.1 Determination of total phenolics, flavonoids, and flavonol content

The total phenolic content of extracts is estimated using a modified method by Yu *et al.* (2002) based on the Folin-Ciocalteu reagent. The concentration of total phenolic compounds in different extracts is expressed as mg of gallic acid equivalents (GAE)/g of dried extract using a standard curve of gallic acid (concentration range, 0.002 to 0.01 mg/ml), described by the equation y = 0.0265x (R2 = 0.9977).

The measurement of total flavonoid content in the investigated extracts is determined spectrophotometrically, according to Zhishen *et al.* (1999). The flavonoids content has been expressed as mg of Rutin equivalents (RE)/g of dried extract by using a standard graph of Rutin, covering the concentration in between 0.02 and 0.2 mg/ml (y = 0.0025x, R2 = 0.9974).

Total flavonols of extracts have been estimated as mg Rutin equivalents (RE)/g extract from the Rutin calibration curve in the concentration range of 0.024 to 0.12 mg/ml (y = 0.0172x, R^2 = 0.9979) using the method of Miliauskas and Venskutonis (2004). Here, y = absorbance and x = concentration. All experiments are done in triplicate.

3.12.2 Antioxidant and free radical-scavenging potential determination (1, 1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging assay)

Scavenging activity on DPPH has been assessed according to the method reported by Blois., 1958[57], with a slight modification. Briefly,100 µl of extracts (0.1 to 0.5 mg/ml) are mixed with 1 ml of a methanolic solution of 0.1 mM DPPH. The mixture has been shaken well and incubated at room temperature for 30 minutes, and absorbance is measured at 517 nm in a spectrophotometer. BHT is used as a standard. The experiment is performed in triplicate and averaged. Percent inhibition is calculated from the control using the following equation:

$$\textbf{Scavenging activity}\ (\%) = (\mathbf{1} - \frac{\textbf{absorbance sample}}{\textbf{absorbance control}}\ \mathbf{100})$$

3.12.3 ABTS radical-scavenging assay

Trolox equivalent antioxidant capacity (TEAC) is estimated as ABTS (2, 20-azinobis-3-ethylbenzothiazoline-6-sulphonic acid) radical scavenging activity according to the method of Re *et al.* 1999[58]. The reagent solution consists of 7 mM ABTS and 2.45 mM potassium persulfate in 100 mM phosphate buffer solution (pH 7.4) and is left to stand for 12 to 16 h at laboratory temperature in the dark to form the ABTS radical cation. A working solution is diluted to absorbance values of 0.7 ± 0.02 at 734 nm with 100 mM phosphate buffer solution (pH 7.4). 10 µl of standards or plant extracts (0.1 to 0.5 mg/ml) are mixed with the working solution (990 µl), and absorbance is measured at 734 nm after 5 min. Trolox is used as a standard. Scavenging activity is calculated as described in the DPPH scavenging assay.

3.12.4 Nitric oxide radical scavenging assay

The nitric oxide radical-scavenging activity of extracts is determined using the method of Sreejayan and Rao., 1997[59]. Sodium nitroprusside in an aqueous solution at physiological pH spontaneously generates nitric oxide, which interacts with oxygen to produce nitrite ions determined by the Griess reagent. 2 ml of 10 mM sodium nitroprusside dissolved in 0.5 ml of phosphate buffered saline (pH 7.4) is mixed with 0.5 ml of extract at various concentrations (0.05 to 0.25 mg/ml). The mixture is incubated at 25^0C. After 150 minutes, 0.5 ml of incubation solution is withdrawn and mixed with 0.5 ml of Griess reagent. The mixture is incubated at room temperature for 30 minutes. The absorbance is measured at 540 nm. BHT is used as a standard. The amount of nitric oxide radical scavenged is calculated as described in the DPPH assay.

3.12.5 Superoxide radical scavenging activity

Superoxide anion scavenging activity is estimated by the modified method of Robak and Gryglewski., 1988[60]. The reaction mixture consisting of 250 µl of 150 µM nitroblue tetrazolium (NBT), 250 µl of 468 µM nicotinamide adenine dinucleotide (NADH), and 250 µl of extract (0.1 to 0.5 mg/ml) is mixed in sodium phosphate buffer (100 mM, pH 7.4). The reaction is initiated by adding 250 µl of 60 µM phenazine methosulfate (PMS) to the mixture. The reaction mixture is incubated at 250C for 5 min, and the absorbance is measured against the corresponding blank solution. Ascorbic acid is used as a positive control. The superoxide radical scavenging activity is calculated using the formula given in the DPPH assay.

3.12.6 Metal ion chelating activity

The chelating activity of the extract on Fe^{2+} is measured according to the method of Dinis *et al.* 1994[61]. 1 ml of extracts (0.1 to 0.5 mg/ml) is incubated with 50 µl of 2 mM ferrous chloride. The reaction is started by the addition of 200 µl of ferrozine (5 mM). After 10 minutes, the absorbance of the ferrous ion-ferrozine complex at 562 nm is measured. Na_2 EDTA served as a positive control. Triplicate samples are run for each set and averaged. The ability of extracts to chelate ferrous ions is calculated using the following equation:

$$\textbf{Chelating activity}\ (\%) = (\mathbf{1} - \frac{\textbf{absorbance sample}}{\textbf{absorbance control}}\ \mathbf{100})$$

3.12.7 Ferric reducing antioxidant power assay (FRAP)

The assay is based on the methodology of Benzie and Strain., 1996[62]. The FRAP reagent consisted of 10 mM 2,4,6-tripyridyl-2-triazine (TPTZ) in 40 mM HCl, 20 mM ferric chloride, and 250 mM sodium acetate buffer (pH 3.6). The FRAP reagent is freshly prepared by mixing TPTZ solution, $FeCl_3$ solution, and acetate buffer in a ratio of 1:1:10. A 100 µl extract solution containing 0.1 mg extract is mixed with 900 µl of FRAP reagent. After the mixture stood at 37ºC for 4 minutes, the absorbance at 593 nm was determined against the blank. Trolox is used as a calibration standard in the concentration range of 0.02 to 0.01 mg/mL ($y = 0.160x$, $R^2 = 0.981$). FRAP values are calculated as mg of Trolox equivalents (TE)/g extract from three determinations and are averaged.

3.12.8 Reducing power assay

The reducing power of extracts is determined as per the method of Oyaizu., 1986[63]. 1 ml of extracts (0.25 to 1 mg/ml) is mixed with 2.5 ml of 0.2 M phosphate buffer (pH 6.6) and 2.5 ml of potassium ferrocyanide (1%). After incubating the mixture at 50ºC for 20 min., 2.5 ml of 10% trichloroacetic acid is added, and then the mixture is centrifuged at 3000 rpm for 10 min. 2.5 ml of supernatant is mixed with 2.5 ml of distilled water and 0.5 ml of $FeCl_3$ (0.1%), and the absorbance is measured at 700 nm and compared with standard ascorbic acid.

3.12.9 Total antioxidant capacity (TAC)

The total antioxidant capacity of extracts is estimated as described by Prieto *et al.* 1999[64]. An aliquot of 0.1 ml of extract is mixed with 1 ml of reagent solution (0.6 M sulfuric acid, 28 mM sodium phosphate, and 4 mM ammonium molybdate) in an eppendorf tube. The tubes are capped and incubated at 95°C for 90 min. After the samples have cooled to room temperature, the absorbance of each is measured at 695 nm against a reagent blank. Gallic acid is used as a standard (0.02 to 0.1 mg/ml), and TAC is estimated as mg GAE/g dried extract from the calibration curve given by equation $y = 0.006x + 0.102$ ($R^2 = 0.93$).

3.13 Hepatoprotective Activities

Since *Doronicum hookeri* is a lever tonic[30], Historically, it has been used to treat liver diseases. Extensive pharmacological work has been conducted to examine the hepatoprotective effects and mechanisms of extracts and compounds extracted from this plant. Ethanolic and aqueous

extracts of the rhizomes of *Doronicum hookeri* showed hepatoprotective activity against CCl_4-induced hepatotoxicity in Charles Foster albino rats of either sex. The study showed that only ethanolic extract at a dose of 500 mg/kg demonstrated partial hepatoprotection against toxicity induced by CCl_4. The level of alkaline phosphatase is similar in both the control and test groups, but there are no significant changes in the values of total bilirubin. The reason for such results may be the short duration of the study[13]. So, further study is required to investigate the hepatoprotective activity.

3.14 Toxicity

Syed *et al.* (2014)[13] carried out an acute toxicity test as per OECD Guidelines 423 using non-pregnant female rats. Three non-pregnant female rats are given the alcoholic and aqueous extracts of *Doronicum hookeri* rhizomes at a dose of 300 mg/kg and are observed for 14 days for any mortality. The same test was then repeated in another group at a dose of 2 g/kg b.w. to confirm the findings. As no mortality is observed on both doses, i.e., 300 mg/kg and 2 g/kg b.w., the LD50 is found to be 2 g/kg b.w. The study revealed that both the extracts of the test drug were found to be non-toxic up to a dose of 2 g/kg b.w.

4. CONCLUSION

Based on the information collected above, it can be concluded that *Doronicum hookeri* has been effectively used in traditional medicines for centuries. Several formulations of *Doronicum Hookeri* are available on a large scale, such as Dawa al-Misk, Laboob Kabir Khas, Khamira Marwareed, Banuskha-e-Kalan, Mufarreh Azam, etc., which are most commonly prescribed by practitioners of traditional medicines. The main purpose of the current review was to provide the reader with a forum to gain a better understanding of the possible therapeutic effects, as described in traditional literature not yet corroborated by modern medicine. The studies conducted on the phytochemistry of *Doronicum hookeri* did not create an important connection between its chemical constituents and their pharmacological effects, and no research was carried out to differentiate between its chemical constituents and the other species of this genus. Therefore, it is suggested that further studies explain these variances among the species. In these studies, an approach should be reflected to detect the exact mechanism of action of the chemical constituents of the species along with safety evaluation in clinical applications. Studies that represent the plant's anti-fungal and antimicrobial effects are considerably restricted to a few fungal and bacterial species. Furthermore, these limited studies are accompanied by no *in-vivo* analysis. It is therefore important to determine the mechanism of action and pharmacokinetics of *in-vitro*, *in-vivo*, and human studies models in the future.

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