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REVIEW OF PROPHETIC FOOD: THE *VITIS* SPECIES

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Abstract

Vitis species or the grapes, possess various natural constituents that can be found in their seeds, leaves and skin extracts. The active chemicals consist of polyphenols, flavonoids, stilbenes, alkaloids and volatile oils. Each of them contributes to pharmacological effects. This study is to highlight the Vitis species that are widely known for their health benefits. The historical uses of this plant include treating stomach pain, injury, and abdominal complaints. In addition, this herb was used as an ointment in treating eye and skin diseases. The medicinal properties of the grapes were reported as anticancer, antioxidant, anti-inflammatory, antimicrobial, cardioprotective, hepatoprotective and neuroprotective. The objectives of this study are to perform a literature search (from 2000 - 2020) and review the shortlisted publications on the Vitis species. From the online articles, the phytochemistry and pharmacological activity of the grapes were mentioned. The review included the traditional uses of the grapes. It is expected that the understanding of the chemical and biological activity of Vitis species may contribute to the development of new drugs.

INTRODUCTION

Vitis species or the grape, belongs to a genus having about 60 species, from the Vitaceae plant family. It is mainly distributed in tropical and subtropical regions, for example, the southern Europe and Western Asia (Nassiri-Asl et al., 2016). This plant species can also be found in several countries such as Iran, Brazil, Chile, United States, Russia, China, Korea and Japan (Chen et al., 2018). Advanced farming techniques are applied, in order to harvest the fruits, locally (Hussin, 2019). Some parts of the *Vitis* plant such as the grape seeds and leaves are widely used for herbal medicine and as a dietary supplement throughout the world (Nassiri-Asl et al., 2016). Moreover, grapes are widely cultivated for the beverage industry, and even for dried grapes or raisins as their beneficial effects are getting attention (Williamson et al., 2010; Moldovan et al., 2020).

The grape plays an important function in our lives. It appears as "Inab" and it is narrated eleven times in the Holy Qur'an, in different verses ('Ali, 1999; Urbi et al., 2014). A number of studies established the pharmacological effects of the grapes or *Vitis* species in promoting human health. It is reported that *Vitis* species possess anticancer, antioxidant, antimicrobial, and anti-inflammatory activity in humans (Tabeshpour et al., 2018). It was determined that *Vitis* species have high antioxidant activity that has the ability to eliminate free radicals (Chen et al., 2018). Furthermore, anticancer activity by *Vitis* species is a promising pharmacological effect, as it is reported to inhibit tumour formation induced by the cancer cell (Nassiri-Asl et al., 2016). Some research showed good antimicrobial activity of *Vitis* species where they are capable of inhibiting gram-negative and gram-positive bacteria (Vijayakumar et al., 2016). Moreover, *Vitis* species are believed to have pharmacological effects such as anti-inflammatory. Studies show that *Vitis* species, especially *Vitis vinifera* (*V. vinifera*), red vine leaves water extracts are capable to inhibit inflammation attenuating gastric inflammation (Nassiri-Asl et al., 2016).

The bioactive compounds found in *Vitis* species have been tremendously getting attention as they contribute significant effects to human health. The compounds are important to give pharmacological effects as mentioned earlier. Many papers showed that bioactive compounds such as polyphenols, flavonoids, and stilbenes can be found in *Vitis* species (Goufo et al., 2020). Polyphenols exist in several parts of the plant of *Vitis* species, especially in the grape where 75% of grape polyphenols can be found in the grape's skin and seed (Vijayakumar et al., 2016). Furthermore, the grape seed contains flavonoids around 4 to 5% and is responsible for the anti-inflammatory activity (Colombo et al., 2019). In addition, stilbenes can be found significantly in woods, canes, stems and roots of *Vitis* species. The stilbenes are reported to induce apoptosis in cancer disease which is on hepatocellular carcinoma cells.

A significant number of scientific papers are mainly focusing on grape and grape seed, but a limited number of those papers reported on other parts of plants of *Vitis* species such as the leaves, cane, wood, and stem (Ben Khadher et al., 2022). The recent information on the availability of bioactive compounds which are phenolic compounds, flavonoids, and stilbenes shows the possible pharmacological effect to the benefit of human health (Rahman et al., 2022). In this review, a thorough understanding of the phytochemicals of *Vitis* species as well as their pharmacological effects will contribute to the scientific knowledge as they are useful to promote human health. In this study, the objectives are to perform a literature search (from 2000 - 2022) and review the shortlisted publications on the phytochemical and pharmacological effects of *Vitis* species.

METHODOLOGY

The methodology involves electronic quest (Mousavi et al., 2015) on both national and international literatures, published between January 2000 to December 2020. The search was based upon online articles such as the US National Library of Medicine (PubMed), EMBASE and Google Scholar, using terms to identify the population involved. The terms for phytochemicals (polyphenols OR flavonoids OR stilbenes OR alkaloids OR volatile oils) and pharmacological effects (antioxidant OR anticancer OR antibacterial OR anti-inflammatory) were used concurrently to the terms for the population. The search filter was developed to mostly include the English language on the search (Table 1). The articles from the references in the retrieved articles were also considered in the literature search.

RESULTS AND DISCUSSION

By using the terms, articles from the databases were retrieved for current research. As a result, about 50 articles were shortlisted, following a manual search via Google Scholar. At first, more than 20000 of the total articles could be retrieved. Then, these articles were screened based on the inclusion and exclusion criteria (Table 1). The criterion included the type of literatures. Original research articles were reviewed, as the primary source. Book series, book, chapter in the book and proceedings of conferences were not involved in this study. Selected subtopics on *Vitis* will be discussed in the following paragraphs, comprising of its traditional uses, pharmacological activities and the natural chemicals. In another note, a quick search from 2000 would reveal around three thousand articles, mentioning on *Vitis* from Islamic perspectives.

Table 1. The inclusion and exclusion criteria.

Criterion	Inclusion / Suitability	Exclusion
Type of the literature	Journals / research articles	book, chapter in a book, proceedings of conferences
Language	English	Malay / Indonesian
Period	2000 - 2022	< 2000
Subject	Medicine, Pharmaceuticals, Phytochemistry and Biological Sciences	Other than Medicine, Pharmaceuticals, Phytochemistry and Biological Sciences

Traditional Uses of Vitis species

Vitis species have been widely used in medicine for having biological constituents with therapeutic uses (Prasansuklab et al., 2021; Pal et al., 2022). Some medicinal uses of *Vitis* species include treating stomach pain, injury and abdominal complaints. In China, the leaves, stems, and roots of *Vitis amurensis* Rupr. (*V. amurensis*), for example, were used for a long time ago as traditional herb. Furthermore, *V. vinifera* was known for a long history as conventional medicine (Badet, 2011). The sap from the grapevines was used as an ointment in treating eye and skin diseases. Similar to *V. amurensis*, the leaves of *V. vinifera* were useful as a traditional plant to treat inflammation, pain and to prevent bleeding. Sore throat can be treated by unripe grapes and constipation by dried grapes. In addition, *Vitis* species are used as a dietary supplement due to the beneficial biological constituents available in seeds, leaves, and fruits. Other than the remedial uses, *Vitis* species especially *V. vinifera*, is cultivated all around the world for making beverages.

Review on The Pharmacological Activity of Vitis species

Antioxidant activity

Antioxidant activity is one of the main pharmacological activity of *Vitis* species. It was reported that the grape seed oil extraction of *V. vinifera* L. was capable to reduce oxidative stress conditions, free radicals scavenging, and inhibit lipid oxidation due to their phenolic constituents. The polyphenols in *V. vinifera* extracts have also been exhibited to modify the

periodontal inflammatory response that causes by pathogenic bacteria. In future studies, researchers are urged to analysed the antioxidant activity of *Vitis* species. The current study and knowledge of antioxidant activity proved significantly its usefulness and beneficial source of antioxidant therapeutic agents.

Anticancer activity

Bioactive compounds in *Vitis* species are associated with anticancer activity. The peel and seed extracts showed anticancer activity, induced apoptosis and apoptotic changes in morphology in human epidermoid carcinoma A431 cell lines. The study shows that the cells treated with the grape seed extracts showed morphological changes, like roundedness, the irregular shape of cells, stressed cells, and cytoplasmic vacuolation because of the stressed cell. It was reported that a potent cytotoxic effect on skin cancer cell lines can be observed with *V. vinifera* seed and peel extracts. A study showed that grape seed oil incorporated as lipid-based nanocarriers has a therapeutic effect on tumour cell inhibition. Although anticancer activity has been shown in many studies, it is still important to have further experiments *in vivo* to discover the anticancer activity on human cancer cells in depth.

Anti-inflammatory activity

Grape seed oil was reported to have anti-inflammatory activity includes in treating chronic diseases. The production of cytokine or the release of arachidonic acid activity is influenced by the phenolic compound found in the grape seed oil (Martin et al., 2020). A study showed the bioactive compounds from leaf and tendrils extracts were able to show significant anti-inflammatory properties. *Vitis* species show significant anti-inflammatory activity that even has been used in the treatment of oral disease. Periodontal disease is associated with the growth of gram-negative anaerobic bacteria. The growth of the bacteria will promote the release of pro-inflammatory cytokines and destroyed the periodontal tissue. According to Bogdan et al., (2020), the resveratrol obtained in the *V. vinifera* extracts was able to reduce the release of pro-inflammatory cytokines when the human periodontal ligament cells were exposed to *P. gingivalis*. In future studies, researchers are urged to analysed the anti-inflammatory activity of *Vitis* species. The benefit could be broadened to treat other inflammatory diseases.

Anti-microbial activity

The health benefits of *Vitis* species were recognized due to the active compounds obtained in the skin, leaves, stems, or tendrils. A study was investigating the compound from grape skin aqueous extract to show the anti-microbial activity. Gram-negative bacteria and gram-positive bacteria such as *Salmonella typhi* H. and *Bacillus subtillis* respectively were challenged with the extract. The anti-microbial activity was observed by the minimum inhibitory concentration through the zone of inhibition (mm) on the agar-well diffusion method. The grape fruit skin aqueous extract shows remarkable bactericidal activity where both types of bacteria showed inhibitory activity on the agar. At the low concentration of extracts of *V. vinifera*, *Salmonella typhi* H. showed the largest diameter of zone of inhibition (Vijayakumar et al., 2016). Piceatannol and *trans*-resveratrol were extracted by 70 % ethanol from the leaf and stem of *V. amurensis* Rupr., prevented the growth of bacteria by 12.5 – 50.0 µg/ml (Chen et al., 2018).

Cardioprotective effects

Several studies showed the cardioprotective effects due to the compound found in grape. Resveratrol was reported to inhibit irreversibly the cyclooxygenase-1 (COX-1), thus prevent the aggregation of platelets in high-risk cardiac patients (Chen et al., 2018). The grape skin extract of *V. vinifera* L. was given during lactation to rats (Nassiri-Asl et al., 2016). The result showed that the extract could reverse the plasma triglyceride levels and insulin resistance, hence reduced the possibility of getting hypertension. Further study should be conducted to investigate the cardioprotective effects of grape for a dietary supplement or the development of a drug.

Hepatoprotective effects

The hepatoprotective effects shown by *V. vinifera* was probably associated with the antioxidant, free radical scavenging, and anti-inflammatory effect. The hepatoprotective effects were reported when some studies combined *V. vinifera* with other herbal medicines in different hepatotoxic models (Nassiri-Asl et al., 2016). Some studies established the hepatoprotective effects of grape due to the anti-inflammatory and antioxidant properties of polyphenols. Grape skin extract was able to improve and protect liver steatosis (Georgiev et al., 2014). The intake of the grape as a nutraceutical may be suggested to prevent chronic liver disease.

Neuroprotective effects

The neuroprotective effects of procyanidins found in grape seed was investigated (Jin et al., 2020). The grape seed procyanidin was associated with antioxidant and anti-inflammatory effects. The result showed the decreased levels of malondialdehyde and lactate dehydrogenase, the biomarker of oxidative stress, hence decreasing the effects of ethanol (Jin et al., 2020). The grape skin and grape seed extracts were able to improve Parkinson's disease *in vitro* (Ben Youssef et al., 2019). The extracts were involved in several cellular targets of Parkinson's disease. The promising neuroprotective effects of *Vitis* species should be a further study *in vitro* and in vivo for other brain diseases (Dwibedi et al., 2022).

Review on The Natural Chemicals in Vitis species

Polyphenols

Polyphenols are secondary metabolites that are most abundant in plants. Polyphenols can be classified into two main families that are diverse in group molecules. The two main families are the flavonoids, based on the common C6-C3-C6 carbon atoms' skeleton, and the non-flavonoids. There are 60-70% of total extractable phenolics in the seeds, 20-30% in the skin, and 10% or less in the pulp. Even though the concentration of phenolics is less in the skin than the seed, there are still a group of phenolics including anthocyanins, flavan-3-ols stilbenes and phenolic acid (Shi et al., 2003). *Vitis* species have the ability to delay initiation and/or retard the progression of normal cognitive decline and Alzheimer's diseases due to polyphenols. It was reported that the pathologies are through the inhibition of neuronal apoptosis triggered by oxidative stressors and pro-inflammatory factors. Polyphenols also contribute to neutralizing accumulated neurotoxins, hence delay the progression of cognitive decline.

The peel and seed extracts of *V. vinifera* were able to impart antiproliferative and apoptotic effects due to their abundant polyphenols content (Grace Nirmala et al., 2018). The study reported that phytochemicals such as flavonoids and tannins show significant cytotoxic effects on the A431 cancer cell line, while it was non-toxic to the normal human keratinocyte cell line. Polyphenols provided significant pharmacological effects that benefit human health. The activity of polyphenols was shown *in vivo* and *in vitro* studies, hence further research are required, as they have potential as functional ingredients in food products and new drugs.

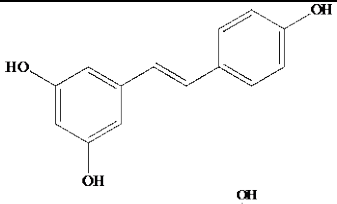
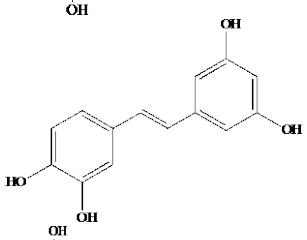
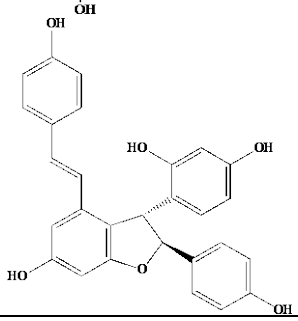
Flavonoids

Flavonoids can be found in the grape. They contribute 70% of the total phenolic content. They are flavan-3-ols (the most abundant), flavonols, anthocyanins, and flavones (the least abundant). Flavan-3-ol is having over 80 % and be stored in the seed. Anthocyanins can be extracted from grape skins (Zhao et al., 2020). They give colour to the red or purple of the grape skin. The total flavonoid content of grape seed could be separated by using acetone and ethanol.

Stilbenes

Vitis species contain stilbenes in various parts of the plant, including the leaves, stem, canes, woods, and roots (Chen et al., 2018) (Table 2). The production of stilbenes is important during a parasitic attack and it happens in both vegetative and reproductive organs. This is because stilbenes inhibit the proliferation of pathogens thus, the concentration of stilbenes increased during fungal infection (Gabaston et al., 2020).

Table 2. Several main compounds of stilbenes (Source: Goufo et al., 2020).

Stilbenes subgroups	Chemical structure	Vegetative organ
Trans-resveratrol (stilbene monomer)		stems, leaves, canes
Trans-piceatannol (stilbene monomer)		leaves, canes
ε-viniferin (stilbene dimer)		stems, canes, woods, roots

Alkaloids

Alkaloids can be found in the *Vitis* species, especially in the seed of grape. It was reported that alkaloids improve wound healing as they possess astringent, antimicrobial and antifungal activity. The wound-healing activity was also investigated on rats. There was a significant increase in wound-healing of excision on the rats. This is because increased content of hydroxyproline of the granulation tissues, a biomarker for tissue collagen, indicates there was an increased synthesis of collagen. (β)-carboline was present in dried grapes and commercial raisins. The main subgroups of β-caroline, norharman and harman (Figure 1) were identified as primary contributors to the inhibition of enzymes, monoamine oxidase (Herraiz, 2007).

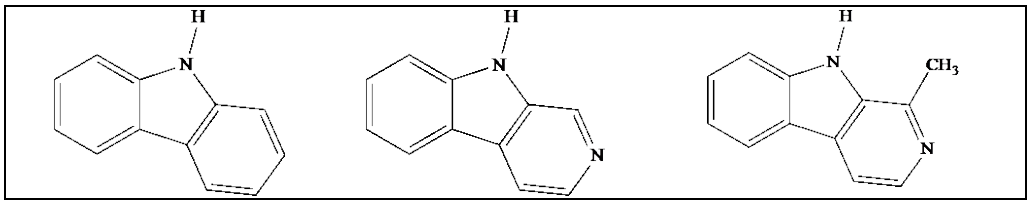


Figure 1. The molecular structure of (β)-carboline (left), norharman (middle) and harman (right) (Source: Herraiz, 2007).

Volatile oils

Vitis species were reported to contain volatile oils. The most abundant volatile oils are linoleic acid and 2,4-decadienal. Many studies established the antimicrobial activity of volatile oils against pathogen bacteria. A study was investigating the antimicrobial activity of volatile oils on gram-positive and gram-negative bacteria. The result showed volatile oils of *V. vinifera* has the lowest antibacterial activity than other volatile oils plant. It was also observed that *Vitis* species have high antimicrobial activity against the gram-positive bacteria than the gram-negative bacteria (Erdogan et al., 2016). In the future, the study on volatile oils of *Vitis* species should be explored more as it has promising antimicrobial activity.

CONCLUSION

A literature review was performed to obtain the updates on the Vitaceae plants. The study showed the scientific evidences about grapes and their nutritional values. In addition, reports specifically on the *Vitis*' stilbenoids were encountered, among other secondary metabolites. Further research would involve the inspection of chemical structures of these natural condensation products involving the dimer, ε-viniferin. From the review, there was no following report on the isolation of the higher polymeric viniferins, in a span of two decades. It is anticipated that the molecules could be identified from the rest of the *Vitis* plants.

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