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FRUIT EXTRACT IN COMBINATION WITH NON-STEROIDAL ANTI-INFLAMMATORY DRUGS TO PREVENT HEPATIC DAMAGE: A POTENTIAL FORMULATION FOR FUTURE

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ABSTRACT

So many statements and research data are mentioned the hepatotoxicity of the Non-steroidal anti-inflammatory (NSAIDs) as a major side effects. Among all other Naproxen sodium is still prescribed and utilized for severe pain. Functionally it is a non-specific inhibitor of the COX-1 and COX-2 and diminishes the action of prostaglandins in human as well as rodents. Side effects with the use of Naproxen sodium are not limited to vomiting, it initiate discombobulating dyspepsia and finally and majorly does liver injury likewise naproxen sodium have negative impact on digestive system, hypersensitivity and ultimately does production of reactive oxygen species which further burden the human as well animals in the form of oxidative stress. Various researcher tried in past to overcome the side effect of naproxen sodium by employing pharmaceutical technologies but still some lacking in positive results. In spite of that, many herbal plant secondary metabolites which have known anticipatory impact on oxidative stress caused by naproxen sodium are utilized to overcome its negative impact but the herbal toxicity is again considerable and questionable status in terms of utilization of herbal plant secondary metabolites in combination with naproxen sodium. Over the counter, the fruits extracts that have good ant oxidative profile are utilized in combination with naproxen sodium in various animal as well as human studies. Competitively fruits are finds a safer place in terms of toxicity like herbal plant extracts. Now, the new studies with formulation development in combination of fruit extract are warranting to overcoming the hepatic side effects of naproxen sodium.

KEYWORD: Naproxen sodium, fruit extract, Hepatotoxicity, Antioxidant activity; Antimicrobial and antiviral effect; Anti carcinogenic activity; Hepatoprotective activity.

INTRODUCTION

Grape fruit juice has been used for hundred years because of their medicinal and nutritional effect they are contain sugar, flavonoids, anthocyanin and proanthocyanins, organic acid, tannin, mineral salt and vitamins, Grape skin, especially red and black species contain antioxidant activity. Grapes are also used as demulcent, laxative and diuretic. It is useful in bilious dyspepsia, hemorrhage, dysuria, in chronic bronchitis, heart diseases and gout. Grape juice is given to children to prevent constipation**.** Dried grapes or raisins are useful in fever, cough, and jaundice and in subacute cases of enlarged liver and spleen. The grape berries are important since they are consumed as fruits, wine juice or rasins and are largely cultivated for the preparations of wine. Antioxidant activity of grapes are due to the presence of antioxidant components such as flavonoids, phenolic acid, anthocyanin and carotenoids (**Kanagarla *et al*., 2013**)

Active constituents

Flavonoids: Grape seeds contain flavonoids (4ñ 5%), including kaempferol-3-O-glucosides, quercetin- 3-O-glucosides, quercetin andmyricetin. Polyphenols: Grapes are rich in polyphenols and)-epicatechin-3-O-gallate, procyanidins–)- epicatechin,(–60ñ70% ofgrape polyphenols are foundin grape seeds. The grape seedpolyphenols are flavan-3-ol derivatives. The major compounds are (+)-catechins, dimers(B1-B5), procyanidinC1, and procyanidinB5-32 -gallate. Grape seeds contain procyanidins or proanthocyanidins (mostly hexamers). All of the acylatedprocyandins of grape seeds areesters of gallic)- epicatechin-3-O-gallate, 14 dimeric, 11 trimeric, andonetetramericprocyanidin have also been reported. Anthocyanins:

Theanthocyanins that have been–)-epicatechin, and (–acid **(Fuleki and Silva, 1997);** however, monomers of(+)-catechin,(reportedfor V. Viniferainclude 3-glucosides, 3-acetylglucosides, 3-coumaroylglucosides, 3- caffeoylglucosides, 3,5-diglucosides, 3-acetyl-5-diglucosides, 3-coumaroyl-5-diglucosides, and 3- caffeoyl-5-diglucosidesofcyanidin, delphinidin, peonidin, petunidin, andmalvidin. Stilbenederivatives: Trans-Resveratrol (trans-3,5,40-trihydroxystilbene) has also been reported in grapes fruit.

Phytochemicals compound of *vitis vinifera L.*

These plants include a variety of bioactive molecules called Phytochemicals that are advantageous to people. Numerous phenolic substances and aromatic acids are present in *V. vinifera L*. throughout the plant. Stilbene, flavonoids, proanthocyanins, hydroxybenzoic acid, and hydroxycinnamic acid are the primary grape mixes. Fruit grapes are a good source of protein, lipids, anthocyanins, flavonoids, stilbenes, phenolic acids, and vitamin C. **(Insanu *et al*., 2021).**

According to Esatbeyoglu *et al*., (2016), grape root extract contained the stilbenoid chemicals resveratrol, vitamins A and B, picaetannol, and miyabenol C. Trans-pieced, cis-pieced, vitriol B, viniferether A, and viniferether B, ampelopsin C, ampelopsin E, hopeaphenol, and isohopeapheno are further stilbenoid chemicals found in grape roots.

Traditional uses of *V. vinifera L.*

Grape seeds contain 6–20% oil, which is used for food purposes, soap, and as a substitute for linseed. The leaves of this and other species are eaten in other cultures. The sap of young branches is used as a remedy for skin diseases., Used in diarrhea. Raw fruit juice is astringent, used in throat infections. dry fruits are cool, sweet, purgative, useful in stomach, thirst, heat of the body, cough, hoarseness, and intake and gout diseases. Turkey's many areas, including Malatya, Elaz, and Manisa, use grapes as traditional medicines. While grapes were advantageous for anemia in the Elaz area, they were advantageous for blood formation in the Malatya region. For the inhabitants of Manisa, grape parts, including the seeds, branches, fruit, dried fruit, leaves, and latex, can be used as carminatives and as a treatment for bronchitis, anemia, colds, and allergies. Grapes (*V. vinifera L.*) are commonly utilized in traditional medicine in Pakistan. The grapes are consumed as carminatives in Pakistan's Northwest. In the Sudhanoti district of Pakistan, the leaves and whole grapes can be used to purify the blood, treat phlegm, and alleviate thirst **(Insanu *et al*., 2021).**

Geographical Distribution and Cultivation of *Vitis Vinifera L.*

Vitis vinifera L. is largely distributed and cultivated approx. all over the world the countries given below are the major cultivator of the *Vitis vinifera L*. China, India, Iran, Egypt, Turkey, Brazil, Mexico, Central And Southern Europe, Western Asia (including Anatolia, Caucasus, Middle East, China), Northern Mediterranean Coast, Africa, South Africa, North Africa, California, Michigan, New Mexico, New York, Oregon, Washington State, British Columbia, Ontario, Quebec, Chile, Argentina, Uruguay, and Peru are all places where *Vitis vinifera* is grown. Most wine is made in Germany, France, Italy, Canada, the United States, and New Zealand. Iran, Turkey, India, and the United States are just a few of the nations that produce raisins **(Parihar and Sharma 2021).**

Botanical description of *vitis vinifera L.*

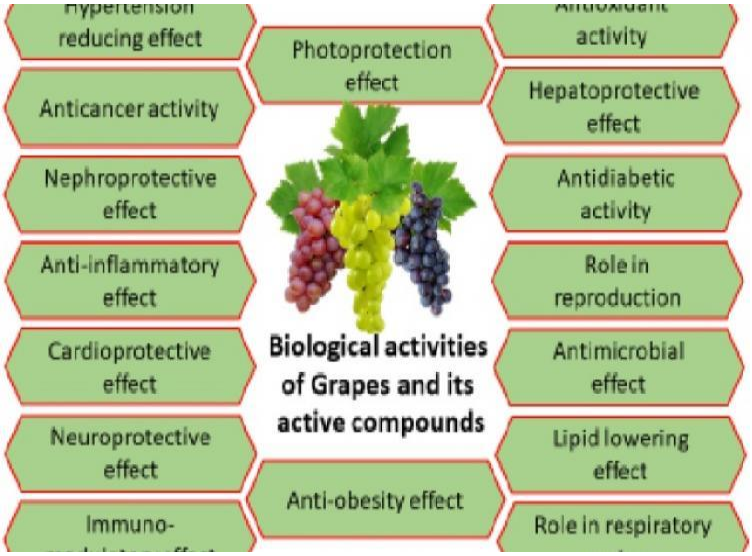
1.	Kingdom	Plantae
2	Clade	Tracheophytes
3	Clade	Angiosperms
4	Clade	Eudicots
5	Clade	Rosid's
6	Order	Vitaes
7	Family	Vitaceae
8	Genus	Vitis
9	Species	*Vitis vinifera*

Pharmacological activities

Antioxidant effects: Antioxidant and free radical scavenging properties are present in grape seed extract. The impact of recycling and saving Alpha-tocopherol was established in phosphatidylcholine liposomes and red blood cells by procyanidins from V. vinifera seeds. In addition to scavenging free radicals, procyanidines also significantly and non-competitively inhibit the activity of xanthine oxidase, the enzyme that triggers the oxy-radical cascade.[8] In one investigation, modest quantities of grape seed proanthocyanidins (2 mg/ l) reduced polyunsaturated fatty acid peroxidation. Further research has verified that grape seed proanthocyanidinextract (GSPE) (50 mg/l) offered superior free radical protection than vitamins C and E in an in vitro free radical scavenging experiment. Moreover, as compared to other antioxidants, GSPE (100 mg/kg) offered appreciable protection against the oxidative damage caused by 12-O-tetradecanoylphorbol-13-acetate (TPA). ProcyanidinB4, catechin, and gallic acid were also reported to be effective cellular preventative agents against DNA oxidative damage at low concentrations (10 mol/l and 25 mol/l). Certain substances, however, may result in cellular DNA damage at increased amounts (150 mol/l). In a similar

vein, GSPE displayed significant antioxidant protection against oxidative injury in rat leukocytes. Combining grape seed extract (75 mg/kg) with marjoram volatile oil reduced the harmful effects of ethanol toxicity on the tissues of the male reproductive system, the liver, and the brain by preventing oxidative damage. Rats were given ethyl alcohol (10ml/kg body weight, 25%v/v) daily orally by gavage for 10 weeks as part of this investigation. Resveratrol (10 mol) pretreatment also inhibited ethanol-induced disruption of embryonic development in blastocysts and ESC-B5 embryonic stem cells. Due to its powerful antioxidant properties, resveratrol has also shown protective effects against ischemia reperfusion in the skeletal muscles of rats.

Effect on the liver: It has been demonstrated that pre-exposure to grape seed extract (3 or 7 days, 100 mg/kg, orally), followed by hepatotoxic dosages of acetaminophen (400 and 500mg). Significantly reduced acetaminophen-induced hepatic DNA damage, apoptotic and necrotic liver cell death, and offset alterations in bcl-XL expression in mice caused by acetaminophen. In one study, grape seed extract (50 mg/kg daily orally for 28 days) guarded against oxidative liver injury after bile duct ligation in rats. Also, administrations of grape seed extract at a concentration of 50 mg/kg/day orally for 15 days prior to ischemia/reperfusion injury, followed by a second administration prior to the reperfusion period, reduced rat liver ischemia/reperfusion injury.



Cardio protective effect

Standardized grape extract (100 and 200 mg/kg) taken orally provided considerable cardio protection by enhancing post-ischemic ventricular recovery and decreasing myocardial

infarction. rats with infarction. Grape seeds (7 g/ml) caused 77% of the endothelium-dependent relaxation in an ex vivo study using rat aorta rings, while grape seed extract (30 g/ml) and grape total (7 g/ml) caused 84 and 72%, respectively. Dietary grape seed tannins (2% monomers or 2% polymers, 3 or 9 weeks) significantly reduce intestinal cholesterol absorption and increase bile acid excretion in rats, which results in improved reverse cholesterol transport. The supplementation of procyanidins in rats and rabbits decreased the damage caused by ischemia/reperfusion to the heart, and this was accompanied by an increase in plasma antioxidant activity. Also, by layering on the surface of coronary endothelial cells and boosting endothelial NO-synthase-mediated relaxation in human internal mammary aortic rings, it was able to stop a peroxynitrite attack on vascular cells. Nonetheless, it was demonstrated that the moderate circulatory relaxations brought on by catechin and epicatechin do not depend on endothelium but rather are brought on by Anthocyanins and grape seed procyanidin were both connected to the health of the endothelium and the production and release of nitric oxide (NO). Blood vessels relaxed in a manner that was dependent upon endothelium due to polyphenolic chemicals in grape seed extract. It was hypothesised that the redox-sensitive activation of the AKT/PI3 kinase signalling pathway that led to the phosphorylation of eNOS-rabbit aortic rings was the mechanism by which the endothelium-dependent relaxation elicited by the grape seed extract was mediated. Similarly, a grape seed extract high in proanthocyanidins protected the heart from reperfusion-induced 178 damage.

Actions that are Antimicrobial and Antiviral effect

There have been reports of antimicrobial action in a number of grape components, including gallic acid, hydroxycinnamicacids, and flavanols.9 \s, trans-resveratrol, and \stannins. Moreover, grape seed extract (1%), according to reports, exhibits antilisterial effect. During 10 minutes, theseed and skin of Ribier grape extracts reduced the amount of L. monocytogenes from 106107CFU/ml to undetectable colonies.

Anti-carcinogenic effects

A polyphenolic fraction derived from grape seeds or commercial grape seeds used topically provided extremely excellent defence against phorbol ester-driven tumour promotion in chemically generated mouse skin cancer. Theprocyanidins' strong antioxidant activity may be substantially to blame for this impact. Recent research on mixed polyphenolic fractions on. A human DNA topoisomerase II assay for cancer chemoprevention using a toyopearl matrix

(TP-2, TP-4, and TP-6) from grape cell culture as powerful catalytic inhibitors. Treatments that combined anthocyaninrichfractions (TP-2; 0.5 or 2.0 Ïg of dried \smaterial/ml), fractions containingcatechins, procyanidin \sdimers, and flavanones (TP-4; 0.25 Ïg of dried material/ml), and/orfractionsenrichedwithprocyanidin oligomers and polymers (TP-6; 0.15 or 0.5 Ïg of dried \smaterial/ml) showedadditiveeffectstoward catalytic \sinhibition of the enzyme. When evaluated on malignant cell lines, the procyanidin-rich fraction TP-6 and its subfractions were specifically cytotoxic (maximal toxicity: 67.2%; ED (50): 50.5 M). Moreover, the 25 g/ml red grape skin polyphenolic extract inhibited and decreased the basal motility of cancer and endothelial cells, reversed the chemotactic effects of sphingosine-1-phosphate (S1P), and prevented and reduced angiogenesis in the Matrigel model (VEGF).

DISCUSSION

Combining fruit extracts with non-steroidal anti-inflammatory drugs (NSAIDs) to prevent hepatic (liver) damage is an interesting concept that warrants discussion. Hepatic damage is a concern when using NSAIDs, so exploring complementary approaches to mitigate this risk is valuable. Many fruits contain antioxidants like flavonoids, polyphenols, and vitamins that have potential protective effects on the liver. These compounds could counteract the oxidative stress induced by NSAIDs. Some fruits possess anti-inflammatory properties of their own, which could complement the action of NSAIDs, potentially allowing for lower NSAID doses and reducing their associated hepatic risks. Discuss the findings of preclinical studies or in vitro experiments that have explored the hepatoprotective effects of specific fruit extracts in combination with NSAIDs. mention any ongoing or completed clinical trials that investigate this combination and their outcomes in terms of liver protection and safety. Consider the optimal dosages and formulation methods for this combination. Should it be a dietary supplement, a prescription medication, or an over-the-counter option fruit extracts might protect the liver from NSAID-induced damage. This could include reducing oxidative stress, enhancing liver detoxification pathways, or modulating inflammation.

CONCLUSION

In summary, grape fruit juice its bioactive com- pounds have several pharmacological activities such as antioxidative, anti-inflammatory and antimicrobial activities, as well as in vitro activity against several can- cer cell lines and Hepatoprotective and cardioprotective effects. Itseemsthat grape juice extract and its active components such asproanthocyanidins, resveratrol, and quercetin are potent antioxidants.The consumption of grapes and grape juice

islikelyto have positive effects on human health and especially in postmenopausal women. These resultssuggestthat grape seeds and their active componentsshould be studied inmore detailfor development as agentsto assist in the treatment of car- diovascular, gastrointestinal, andneurodegenerativedis- ease.

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