JOURNAL OF NATURAL REMEDIES
DOI: 10.18311/jnr/2024/43516

SHORT REVIEW

Watermelon: An Exploration of Possible Therapeutic Benefits

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Abstract

Watermelon (*Citrulluslanatus*) is a widely cultivated fruit appreciated for its sweet taste, abundant water content, and low-calorie nature. In certain Asian regions, watermelon seeds are utilised for snacks and flour. The oil content in these seeds' ranges from 10% to 35%, varying with the genotype. Extracts from the seeds were obtained using hot water, cold water, ethanol, and methanol. Standard microbiological methods were employed to verify the viability and identity of test organisms. Watermelon seed oil is recognised as a rich source of essential fatty acids, carotenoids, tocopherols, thiamine, flavonoids, riboflavin, and other phenolic substances. The quantities of these components vary based on the watermelon variety and extraction method, with linoleic acid being the predominant fatty acid irrespective of the variety. This review aims to raise public awareness about the characteristics and potential benefits associated with watermelon seeds. Substantial research indicates that watermelon seeds possess anti-diabetic, anti-microbial, anti-inflammatory, and cardioprotective properties, positively influencing growth. Following a thorough toxicological examination, animal studies, physicochemical assessments, and nutritional analyses, it is strongly recommended to promptly explore the commercial potential of this product.

Keywords: Anti-diabetic, Anti-Microbial, Anti-Inflammatory, Cardioprotective, Fertility Enhancer, Watermelon Seeds

1. Introduction

A delicious and refreshing fruit, watermelon (*C. lanatus*) is a member of the Cucurbitaceae family, which also includes cucumbers, pumpkins, and squash[1]. Famous for its juicy, sweet, bright red flesh, watermelon is a summertime favourite enjoyed all over the world[2]. There are many different types of watermelon, and they all have unique flavours, textures, and looks[3]. Watermelon seeds are tiny, brown or black and embedded in the flesh of the fruit. Watermelon seeds are considered an annoyance when eating the fruit[4]. However, some people choose to consume them since they may have health benefits. Watermelon seeds are suitable for consumption and can be enjoyed in their raw, roasted, or sprouted forms, with roasted seeds being a popular snack in certain cultural traditions[5]. This tropical plant thrives in warm climates and is primarily propagated through seeds.Optimal growth conditions involve ample sunlight and temperatures exceeding 25°C. Well-suited environments for watermelon cultivation are characterized by fertile, well-drained soils with a slightly acidic pH. Despite its minimal calorie content, watermelon is nutrient-rich and functions as a revitalizing thirst quenche[6]. While generally safe, those with seed allergies should exercise caution, emphasizing thorough chewing, especially when consuming larger quantities due to the seeds' toughness. Watermelon, known for its low calorie and fat content, stands out as a hydrating and refreshing snack. It serves as a valuable source of essential vitamins, including vitamin C and vitamin A, as well as minerals like potassium. The red tint of watermelon flesh is attributed to the antioxidant lycopene, a compound also seen in tomatoes[7].

Traditionally, the seeds, rind and peels of watermelon are often discarded or utilized as animal feed[8]. However, emerging research suggests that these commonly overlooked parts offer various health

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Article Received on: 09.04.2024 Revised on: 05.09.2024 Accepted on: 13.09.2024

benefits. The peels, for instance, are recognized for their analgesic properties[9], the rind exhibits vasorelaxant action[10], and the seeds play a role in regulating blood sugar by facilitating insulin release from the islet of Langerhans' β-cell[11]. Despite these identified benefits, there remains a lack of comprehensive knowledge about their broader biological impacts. Therefore, it is imperative to conduct further research to explore and understand the health advantages associated with these underutilized components. This research can contribute to raising consumer awareness about the diverse health benefits offered by various parts of the watermelon.

Studies have shown that watermelon (*C. lanatus*) seeds, which are frequently thrown away after eating the fruit, are an important source of nutrients and health advantages for people. The Folin-Ciocalteau test, the potassium permanganate titration method, and the iron (III) chloride titration method were utilized to determine the amounts of tannin, phytate, and oxalate, respectively[12]. The indigenous population has a longstanding history of utilizing plant-based oils for a variety of purposes, including food, energy, medicine, and cosmetics. The rising global population has led to an increased demand for edible oils, subsequently driving up their prices. This has prompted a search for alternative sources of oil, particularly in developing nations. There are numerous undiscovered plant seeds known for their high oil content, making them suitable for both industrial and culinary applications. Watermelon seed oil is an underutilized product that has a high linoleic acid concentration (around 64.5-67.2%)[13]. Furthermore, there needs to be a concentrated effort to increase the use of these unusual food wastes to reduce the environmental risks connected with solid waste[6,14,15].

2. Taxonomical Classification[15]

Kingdom	*Plantae*
Class	*Equisetopsida*
Subclass	*Dilleniidae*
Order	*Cucurbitales*
Superorder	*Violence*
Family	*Cucurbitaceae*
Genus	*Citrullus*
Species	*C. lanatus*

3. Botanical Description

The Cucurbitaceous family includes the vine-like watermelon plant, which is an annual herbaceous plant. Usually spreading out across the ground, it produces huge, deeply green leaves that are lobed. Tendrils on the plant help with climbing and anchoring[16]. Yellow flowers appear during its flowering season, and the same plant might have both male and female blooms. The characteristic watermelon fruits emerge from the female flowers after successful pollination[17]. Depending on the kind, these fruits can vary in size, shape, and colour; nevertheless, they frequently have a green rind with stripes that are lighter or darker. The interior flesh is delicious and sweet, with a pink to crimson colour and dark seeds scattered throughout, however occasionally it is seedless. Since watermelon plants need warm weather, lots of sunshine, and well-drained soil to grow, they are frequently grown in areas with a Mediterranean environment[4-8,16]. In India, watermelon is renowned under various names depending on the state and languages such as *Tormuj* (Bengali), *Tarabuuja* (Punjabi), *Kadu vrindavan* (Marathi), *Palam* (Tamil), *Indrak* (Gujarati)[5,13].

4. Nutritional Value

Watermelon fruits comprise various bioactive substances, such as glycosides, carotenoids, flavonoids, alkaloids, carbohydrates, fatty acids, and essential oils[18]. Cucurbitacins, a diverse group of bitter compounds found in watermelon, have garnered attention due to their pharmacological properties that may inhibit the development of cancer[19]. Watermelon is a natural reservoir of citrulline, a non-protein α-amino acid, known for its antioxidant properties and ability to promote vasodilation[20]. Watermelon is a valuable reservoir of vitamins B, C and E, along with essential minerals like phosphorus, magnesium, calcium, and iron[21]. Carotenoids such as lycopene and β-carotene contribute to the vibrant red and orange hues of the fruit, respectively[5]. The sweetness of watermelon primarily stems from a blend of sucrose, glucose, and fructose. Sucrose and glucose make up 20–40%, while fructose constitutes 30–50% of the total sugars in a ripe watermelon[9-12,22-24].

5. Pharmacological Activity of Watermelon

5.1 Antimicrobial Activity

Chronic and infectious diseases constitute a burden on developing nations. It is critically necessary to find cost-effective solutions to handle this elevated combined disease load because the increased disease burden has the potential to collapse the already vulnerable healthcare systems in this world[25]. Numerous studies have demonstrated the antibacterial capabilities of alkaloids, which are important medicinal chemicals present in plants[26]. Alkaloids have also been found in watermelon pulp, peels, and seeds, according to past research[27]. Furthermore, strong antimicrobial medicines that are efficient against microbial strains that cause disease are essential for fighting infectious disorders. As a result, research into new antimicrobial drugs is continuing. Products made from plants provide an answer to this problem because they have been shown to possess antioxidant and antibacterial qualities[27]. The effective extraction and assessment of antibacterial and antioxidant properties from these plants is essential to the advancement of their use in the pharmaceutical industry. Triterpenoids (Cucurbitacins), which have only been found in the pulp and seeds, have shown antibacterial qualities[28]. Other groups of phytochemicals such as saponins and tannins are known to have anti-bacterial and anti-fungal properties. These results suggest that the peel and seeds of the watermelon plant, which are usually ignored, may have medicinal value and should not be ignored[29,30].

5.2 Cardioprotective

For heart health, a diet high in fruits, vegetables, whole grains, lean proteins, and healthy fats is usually advised[31]. Because of their high nutritional value, watermelon seeds may be beneficial for heart health, but further research is necessary to determine the precise effects. Several amino acids, including arginine, which is necessary for the synthesis of nitric oxide, can be found in watermelon seeds. Following consumption of watermelon, argininosuccinatelyase (ASL) and argininosuccinate synthase (ASS) can convert L-citrulline into L-arginine, raising the level of plasma L-arginine, which endothelial cells can use to produce Nitric Oxide (NO)[32]. Therefore, NO has the potential to enhance vascular health indices, including biomarkers, arterial stiffness, blood pressure, and endothelial function[33]. However, culinary technologies are warranted to make watermelon products with higher L-citrulline content because it takes a large volume of watermelon to get the effective L-citrulline dosage[34]. To improve blood flow and blood pressure regulation, nitric oxide can assist relax and dilate blood vessels. Certain heart-healthy lipids, such as monounsaturated and polyunsaturated fats, can be found in watermelon seeds. Protein, which is necessary for maintaining heart muscle tissue as well as general health, is found in abundance in watermelon seeds. Magnesium, a necessary mineral for controlling blood pressure and preserving a normal cardiac rhythm, is present in watermelon seed[35]. Antioxidants like vitamin E, which can lessen oxidative stress and inflammation and possibly improve heart health, are also present in watermelon seed[17-20,36].

5.3 Anti-inflammatory Activity

Because of their nutritional makeup, watermelon seeds, like the fruit itself, may have anti-inflammatory qualities. They are an excellent source of protein, which is necessary for many body processes, including the synthesis of chemicals and enzymes that control inflammation[37-39]. A small quantity of omega-3 fatty acids, such as Alpha-Linolenic Acid (ALA), which are well-known for their capacity to lessen inflammation in the body, are also present in watermelon seeds[40,41]. These seeds also contain antioxidants, including vitamin E, which help reduce inflammation and fight oxidative stress. A range of amino acids are also present in watermelon seeds, including arginine, which is a precursor to nitric oxide and has vasodilatory properties that may help reduce inflammation[40,42]. Watermelon lycopene demonstrated a dose-dependent reduction in the expressions of iNOS and COX-2 mRNA levels as well as their corresponding proteins. This indicates that watermelon lycopene possesses potent anti-inflammatory properties[42].

5.4 Anti-diabetic Activity

The utilization of natural products for the prevention and treatment of various pathologies is consistently growing on a global scale. A methanolic extract from *C. lanatus* seeds was shown by Magdalene Omigie and colleagues to be effective in controlling blood glucose levels and electrolyte parameters (Na^+, K^+, HCO^{3-} and Cl^-) in a group of fifteen female Wistar rats. To induce diabetes, an intraperitoneal injection of 60 mg/kg of streptozotocin was administered. According to Omigie *et al.*, the reduction in plasma glucose levels was attributed to either enhanced hepatic glycogen synthesis or the promotion of insulin secretion from pancreatic β-cells[42,43]. One of the main causes of the beginning of diabetes complications is protein glycation. WMSE (Watermelon seed extract) significantly reduces the effects of oxidation-induced protein glycation and degradation[44]. Additionally, the results suggest that WMSE functions as a free radical scavenger and metal ion chelating agent, hence impeding the formation of Advanced Glycation End-products (AGEs). This implies that WMSE could help treat diabetes-related issues and reduce the impacts of hyperglycemia-induced protein breakdown[45]. Watermelon seeds possess dietary fibre, a component recognized for its role in managing blood sugar levels through the deceleration of sugar absorption, thereby contributing to improved glycemic control[46,47]. Furthermore, studies suggest that certain chemicals found in watermelon seeds may have hypoglycemic effects, which could result in a decrease in blood glucose levels. It is believed that the presence of bioactive substances, such as peptides, is connected to these effects[45].

5.5 Fertility Enhancer

The inability of a couple to conceive after a year of consistent, unprotected sexual activity is known as infertility[48]. Males with higher testosterone levels have been linked to greater sexual desire, according to earlier research. Moreover, higher blood sex hormones have been associated with watermelon seed extract administration in male rats[49]. According to experimental results, the administration of watermelon seed extract dramatically improves sexual behaviour. This includes shorter post-ejaculation intervals, reduced latencies for ejaculation and intromission, and greater frequency of mounting and intromission[50]. Watermelon contains steroidal phytochemicals such as arginine, citrulline, saponin and flavonoids that have demonstrated potential results in the treatment of infertility[51]. An experimental study of male rats that were given nicotine and a hydromethanolic extract from watermelon rind had higher secretions of gonadotropin and testosterone as well as better-quality semen[52]. Watermelon seeds are a good source of arginine and citrulline, which are building blocks for the synthesis of nitric oxide, a powerful vasodilator[53]. By raising guanosine monophosphate levels, Nitric Oxide (NO) is essential for penile erection[54]. As long as other production processes are functioning properly, consuming watermelon provides essential components needed for NO synthesis. Additionally, citrulline converts into arginine, a substance associated with an increase in male sperm count[55].

5.6 Hepatoprotective Effect

The liver is an organ of paramount importance which plays an essential role in the metabolism of foreign substances. The liver gets damaged after a high dose of paracetamol which produces hepatotoxicity; it leads to leakage of cellular enzymes into the plasma[56]. The increased level of serum enzymes such as ALT and AST activities and total bilirubin observed in hepatotoxic rats are indicators of liver damage, increased permeability and necrosis of the hepatocytes[57]. The decline in AST and ALT activities following the administration of a high dose of the extract suggests potential liver repair facilitated by *C. lanatus* seed extract in rats. This phenomenon could be attributed to the presence of bioactive compounds in *C. lanatus*, which may have elevated glutathione levels[58]. Glutathione can bind to harmful paracetamol metabolites like N-acetyl-p-benzoquinone imine (NAPQ1), thereby enhancing their breakdown and elimination from the body. Additionally, these compounds might have inhibited the cytochrome P-450 enzyme system, leading to a reduction in NAPQ1 formation from ingested paracetamol[59-62]. The result from the phytochemical studies of the methanol extract of *C. lanatus* seed indicated the presence of terpenoids, alkaloids and flavonoids that may play a role. The elevation in total plasma bilirubin observed in paracetamol hepatotoxic

rats suggested abnormal conjugation of bilirubin by the liver due to generalized hepatocellular damage[58].

5.7 Anti-oxidant Activity

Oxidative stress and an imbalance in antioxidant properties are frequently implicated in the development of cancer and cardiovascular diseases[63]. To counteract this, synthetic antioxidants like butylated hydroxyanisole (BHA) and butylatedhydroxytoluene (BHT) are commonly utilized in the food, cosmetic, and pharmaceutical sectors[64]. Nevertheless, these antioxidants are costly and have been reported to pose risks to human health, leading to adverse effects such as liver damage and potentially causing cancer[65]. The risks and concerns linked to synthetic antioxidants have sparked consumer interest in turning to foods rich in natural antioxidants as a viable alternative. Natural antioxidants are found throughout various parts of higher plants, and those used for medicinal or culinary purposes are particularly valuable as sources of antioxidants. These include essential vitamins like A, E, and C, as well as phenolic compounds such as phenolic acids, flavonoids, lignin, stilbenes, and tannins[66,67]. Additionally, these secondary metabolites also demonstrate a range of beneficial activities, including anti-inflammatory, antibacterial, antiviral, anticancer, and immune-stimulating properties[68]. Polyphenols are also responsible for providing antioxidant properties[69]. A common characteristic of polyphenols is the presence of multiple hydroxyl groups bonded to the benzene ring[70]. The fruit is rich in lycopene, a potent antioxidant that helps neutralize harmful free radicals in the body[18]. The watermelon mesocarp refers to the white-coloured layer of the watermelon rind located between the endocarp and the outer green-coloured skin. This layer contains various compounds, including flavonoids, which are known to act as antioxidants[71].

5.8 Anti-proliferative Effect

Cancer is a major cause of death globally, and the emergence of resistance in cancer cells to current treatments highlights the urgent need for new anticancer drugs[72,73]. Watermelon is rich in lycopene and various other carotenoids, offering potential health benefits for humans[18]. Carotenoids can potentially exert diverse impacts on cancer and its progress[74]. Humans and animals cannot produce carotenoids within them and primarily acquire them through consumption, predominantly from plants, animal-based sources, and seafood. Yellow, orange, and red fruits, along with green leafy vegetables, seaweeds, fish, and eggs, are recognized for their high content of various carotenoid[75]. The substantial intake of lycopene among the participants in the study led to significant anti-cancer effects in multiple cancer cell types, notably in prostate cancer cells[76]. Cucurbitacins also referred to as cucurbitane triterpenoids, possess anti-inflammatory, antioxidant, and anticancer properties[77]. The historical use of cucurbitacins in traditional medical practices across various cultures highlights their significance as therapeutic agents. However, it is recent scientific advancements that have revealed the detailed mechanisms behind their pharmacological effects. Cucurbitacins demonstrate a remarkable capability to regulate important signalling pathways within cancer cells, impacting functions like cell cycle control, apoptosis (programmed cell death), and angiogenesis (formation of new blood vessels)[78,79]. Cucurbitacins play a role in reactivating the apoptotic pathway within cancer cells, which involves activating pro-apoptotic proteins while inhibiting anti-apoptotic proteins. This leads to the targeted destruction of cancerous cells while sparing healthy cells[80]. For instance, cucurbitacin E (CuE) demonstrated the ability to delay the growth of human breast cancer cells in laboratory studies. CuE induced both apoptosis and cell cycle arrest, likely achieved by inhibiting the function of Signal Transducer and Activator of Transcription (STAT3)[80].

6. Toxicity Effect

In moderation, watermelon is generally safe and beneficial, but overconsumption, particularly for people with kidney problems or other pre-existing health conditions, could lead to some negative side effects. The results of the research study raise concerns about human health, especially for people who routinely consume Watermelon Seed (WMS), as it may cause tissue-related injury, specifically to the kidneys and testes. High dosages of these seeds may impair male reproductive capacities in rats, as indicated by a significant reduction in sperm quality. Moreover, ovary weight significantly decreased in female rats fed WMS, emphasizing the necessity for additional research into the potential impact on female reproductive health.

To find a safe WMS consumption level that balances its potential health benefits, further dose-dependent studies over a longer time frame are needed[81].

7. Conclusion

The existing literature highlights the positive impacts of *C. lanatus* (CL), as it has been documented to possess various pharmacological properties that can serve as a supplement against a range of health-related issues. CL contains a variety of nutrients such as vitamin C, minerals, proteins, glycoproteins, carbohydrates, and active phytoconstituents like citrulline, arginine, flavonoids, and saponins distributed throughout its different parts. This nutritional composition may contribute to meeting the requirements for a healthy lifestyle. Notably, *C. lanatus* seeds find use in the preparation of sweets, beverages, and other food products, while the oil extracted from the seeds, pulp, and rind is reported to have applications in cosmetics. Therefore, the entirety of *C. lanatus*, including its seeds, pulp, peel, and leaves, seems to offer benefits not only as a supplement for various health issues but also on a commercial scale. Conducting molecular research on the pharmacological activities of *C. lanatus* could aid in understanding its mode of action.

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