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REVIEW ARTICLE

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Antioxidant Effects of *Syzygium cumini* Fruit Pulp Extract against Cadmium-Induced Reproductive Toxicity

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Abstract
Although there are multiple environmental pollutants, heavy metals such as cadmium (Cd) represent the most serious one because of the oxidative stress they induce. The emerging evidence suggests that herbal medicine has become an essential alternative medical approach due to its natural identity and the lack of deleterious side effects. Many health benefits have been documented to phytochemicals such as flavonoids, polyphenols, alkaloids, and carotenoids, including putative antioxidant impacts thereby alleviating various oxidative stress conditions. *Syzygium cumini* is a type of plant that is rich in a variety of physiological phytochemical compounds. These compounds were observed to be present in various parts of the plant including leaves, seeds, peel, and pulp. Because of these compounds, the fruit of this plant is claimed to have anti-diabetic, anti-hyperlipidemic, antioxidant, hepatoprotective, antimicrobial, anti-inflammatory, antipyretic, antiplaque, radioprotective, neuropsycho-pharmacological, nephroprotective, and antidiarrheal properties as well as the ability to improve fertility in both male and females. The focus of this review is mainly on the antioxidant effects of *Syzygium cumini* fruit pulp extract against the reproductive challenges caused by exposure to cadmium.

Keywords
Antioxidants, Cadmium, Male and Female Fertility, Reproductive Toxicity, *Syzygium cumini*

1. Introduction

Cadmium (Cd) is a heavy metal of the most harmful contamination on environment. It is evidenced to have a significant impact on humans and animals' health. They are at high risk of exposure to Cd since it is not broken down when present in food chains **(ATSDR, 2005)**. In addition, the risk of Cd exposure is ongoing as it has been detected in most common foodstuffs like cereals and vegetables **(WHO, 2019).** Moreover, Cd can also harm humans through smoking; when one pack of cigarettes is smoked per day, about 1–3µg of Cd is absorbed **(Waalkes, 2003).** Cadmium can accumulate in the body due to its lengthy biological half-life (10-35 years), which amplifies its detrimental effects on many body organs **(Genchi et al., 2020).** In this context, long-term exposure to Cd-contaminated water leads to Itai-itai disease (reported in Japan), which is manifested by renal injury and osteomalacia **(Nishijo et al., 2017)**. Cadmium is mostly associated with oxidative stress; it generates many reactive species such as superoxide anion, hydroxyl radicals, and hydrogen peroxide, which causes an increase in lipid peroxidation, DNA alteration, and cell death **(Stohs et al., 2001)**. Several studies confirmed the detrimental effects of Cd on fertility in males **(Elblehi et al., 2019)** and females **(Cheng et al., 2019).**

Several investigations have revealed a vast population of plant-derived compounds known as phytochemicals **(Meybodi et al., 2017)**. These phytochemicals, which include polyphenols, flavonoids, carotenoids, and alkaloids that have a variety of positive health impacts, can be crucial in the breakdown of peroxides by absorbing and neutralizing free radicals **(Jayasree et al., 2022).** *Syzygium cumini* "*S. cumini*" (synonyms: *Eugenia jambolana*, *Syzygium jambolana*, *Eugenia cuminii*), commonly known as jamun, jambul, jambolao, Java plum, Indian blackberry, and black plum, belongs to the family Myrtaceae, is one of the plants that contain a high concentration of phytochemicals **(Baliga et al., 2011),** which, in accordance with epidemiological studies can aid in preventing Cd from harming human's health **(D'Andrea, 2015).**

2. Sources and Exposure to Cadmium

Releasing of Cd in the environment is either through natural or anthropogenic factors. It is normally found as a combination with other compounds such as cadmium oxide (CdO), cadmium chloride ($CdCl_2$), or cadmium sulfide (CdS). It also could be present as an end product that results from treatment of different metals like copper, iron or sulfur **(Chatterjee et al., 2017).** Volcanic discharges, leakage from rocks inside water, and burns of forests are other natural sources of Cd. Additionally, anthropogenic sources include the vapors of cool burning, some pesticides and fertilizers, preservatives of wood, fuel combustion, and plastics, paints and battery industrial activities **(Abd et al., 2011).**

As it may be found in everything, including food, dietary supplements, alcoholic beverages, and tobacco, Cd is a common environmental pollutant. Cd is the most prevalent of the 30 elements found in cigarette smoke, and smokers have approximately twice as much Cd in their bodies as non-smokers do **(ATSDR, 1999).** Most of the time, exposure to Cd happens unintentionally when performing certain jobs, such as working in an industrial setting, ingesting contaminated food or water, or breathing polluted air. Additionally, in recent decades, improvements in the production of CdSe/CdTe-based photovoltaic solar cells used as a substitute energy source and CdSe/CdTe-based nano-materials utilized in biological applications may potentially be responsible for the rise in Cd exposure in people **(Fowler, 2009)**. Animals that graze on polluted plants will also accumulate Cd in their organs, including the liver, kidney, and testes which are consequently considered a hazard cadmium source for humans.

3. Cadmium Effects on the Reproductive System and Fertility

Environmental exposure to Cd has been linked to reproductive and developmental damage, according to epidemiological research **(Massányi et al., 2020)**. Numerous studies have shown the negative effects of Cd on the reproductive system **(Amr et al., 2023)**. Cadmium toxicity in testes **(Xu et al., 2017),** and ovaries **(Liu et al., 2019)** has been evidenced. Cadmium has the ability to reduce fertility by negatively affecting the various parameters of the reproductive system **(Abdel-Wahab et al., 2021)**, and this can occur by induction of oxidative stress in tissues, which lowers the capacity of tissue antioxidant enzymes and increases the production of ROS **(Xu et al., 2017),** resulting in infertility due to defective germ cell production **(Liu et al., 2021)**,and this is what Cd does **(Ali et al., 2022)**.

Male infertility caused by Cd is linked to histological issues, poor sperm quality, and impaired spermatogenesis **(Hassanin et al., 2019)**.Cadmium causes significant structural damage to the blood-testis barrier, seminiferous tubules, and Sertoli cells (SCs)**.** Cadmium also alters the function of somatic cells and germ cells, producing infertile or subfertile males **(Ali et al., 2022).** It has also been shown to decrease DNA integrity in Leydig cells and testosterone synthesis in vitro **(Zhu et al., 2020).** In females, Cd adversely affects rats' ovarian structure and estrous cycle length **(Amr et al., 2023)**, interfering with gonadotropin hormones and lowering blood FSH and LH levels **(Ruslee et al., 2020)** and decreasing both folliculogenesis and ovarian follicle reservoir **(Saedi et al., 2020)**. In rat ovaries, Cd reduces antioxidants and raises levels of MDA and hydrogen peroxide (H_2O_2) **(Nna et al., 2017)**. Depending on age, exposure to Cd in the environment can change the amount of anti-mullerian hormone (AMH) and ovarian function **(Massányi et al., 2020)**.

4. Biochemical Mechanism of Cadmium-Induced Injury on Male and Female Rats' Fertility

It has been demonstrated that Cd directly causes toxicity in the cells of spermatozoa, Leydig and Sertoli cells. Moreover, exposure to Cd leads to arrest in the development of ovaries **(Cheng et al., 2019)**. This is accomplished by indirectly raising reactive oxygen species (ROS) as a pro- apoptotic agent via an inflammatory process and by altering the hypothalamus-pituitary-gonadal axis. The formation of ROS which becomes harmful if not eliminated by antioxidants is linked to the majority of the reprotoxic consequences caused by Cd exposure **(Ikokide et al., 2022).** Reactive oxygen speciesor free radicals are atoms or groups of atoms having one or more unpaired electrons that exist in a free form **(Lushchak, 2014)**. Lipid free radicals, superoxide anion radicals, hydroxyl radicals, hydroperoxy radicals, peroxy radicals, and nitric oxide are some examples of free radicals that can develop **(Zeb, 2015)**. Chain reactions involving free radicals begin with a mechanism known as the initiation reaction. Following that, the free radical spreads by colliding with other molecules. The termination step refers to the ultimate reactions **(Ahmadinejad et al., 2017)**. Free radicals can have lipid, protein, carbohydrate, organic, inorganic, or metal atoms as their substrate (R). Free radical production happens frequently during cellular biochemical reactions. But as the quantity of free radicals rises, metabolic pathways become unbalanced, and oxidative stress results. Thus, the antioxidant agents are required to combat oxidative stress **(Zeb, 2018)**.

Reactive oxygen species production has been linked to Cd-induced infertility in several investigations. Only when the antioxidant system fails to maintain homeostasis can ROS levels rise to an unhealthy level. The lack of a strong antioxidant system causes a rise in ROS and leads to oxidative stress (OS). Oxidative stress adversely impacts the development, apoptosis, and functioning of somatic and sperm cells **(Morielli and O'Flaherty, 2015)**. In agreement with the previously mentioned studies, Cd has the potential to enhance lipid peroxidation, DNA damage, and protein degradation by inducing oxidative stress in testes and this was confirmed in many studies which explained the negative effects of oxidative stress on antioxidant system parameters represented in a decreased levels of SOD, catalase and glutathione, in addition to increased levels of oxidants such as MDA and lipid peroxide **(Ali et al., 2022)**. Recent research confirmed the oxidative stress caused by Cd in testes of rats through measurement of different parameters such as decreased serum testosterone, protein levels of steroidogenesis and spermatogenesis, in addition to high levels of cytochrome C and caspase 3 **(Venditti et al., 2023)**. Also, the bioaccumulation of Cd in ovaries led to oxidative stress when female rats received cadmium chloride in a dose of 5mg/kg BW/day **(Nna et al., 2017)**. Another study confirmed the occurrence of oxidative stress in the ovary following Cd exposure which was represented by increased oxidative markers such as MDA and hydrogen peroxide and decreased levels of antioxidant indicators as catalase and reduced glutathione **(Khaled et al., 2022)**. Moreover, Cd exposure in female rats led to alterations in their reproductive performance which was **(Zhang and Lin, 2009)** manifested by reduced levels of estrogen and progesterone **(Nasiadek et al., 2018)** as well as diminished levels of LH and FSH **(Ruslee et al., 2020).**

5. Syzygium cumini

5.1. Biological Classification of *Syzygium cumini*

Syzygium cumini is classified as a plant class of Angiosperms, Kingdom of Plantae, Order of Myrtales, Family of Myrtaceae, Genusof *Syzygium*, and species of cumini. It is called Jaman or Jamun in Hindi, Jamboo or Java Plum in English, and *Syzygium cumini* L in Latin **(Kumar and Singh, 2021).**

5.2. Plant Parts and their Phytochemical Composition

Different physiologically active substances can be found in many portions of a plant, including the leaves, seeds, peel, and pulp **(Huang et al., 2022)**. A study found that the components of *S. cumini* that have antioxidant activity are highly diverse **(Dissanayake et al., 2022)**. The Jamun tree contains a variety of compounds including anthocyanins, glucosides, ellagic acid, isoquercetin, kaempferol, and myricetin. The plant's enormous potential as a source of food and medicine is further enhanced by the abundance of bioactive chemicals found in Jamun roots, barks, leaves, and stem, including tannins, phenols, lipids, alkaloids, and flavonoids **(Singh et al., 2019)**. Quercetin, crategolic acid, betulinic acid, myricetin, and kaempferol are found in the leaves of the *S. cumini* plant. Primary and secondary metabolites found in *S. cumini* include proteins, carbohydrates, amino acids, alkaloid compounds, phenolic substances (gallic acid, caffeic acid, ellagic acid), flavonoids (quercetin, myricetin, kaempferol), and anthocyanins **(Qamar et al., 2022)**. *S. cumini* contains phenolic components called flavonoids (anthocyanins), flavonols (quercetin, myricetin), and flavanols, which together make up the bioactive ingredients (catechins) **(Baliga et al., 2011)**. Jamun fruit has been recognized as a nutraceutical fruit due to the presence of antioxidants such as ascorbic acid, anthocyanins and total phenols **(Singh and Sharma, 2020)**. There are high levels of phenolics in fruit extract of *S. cumini* **(Wasswa et al., 2019)**. *S. cumini* seed extract is a good source of natural antioxidants **(Wasswa et al., 2019)**. Natural antioxidative products of jamun seeds are safe, available, cheap and more effective than synthetic drugs **(Adedapo and Ogunmiluyi, 2020).** Seed extract had a much higher total phenolic, flavonoid, and tannin content and stronger antioxidant capabilities **(Ahmed et al., 2021)**. Flavonoids with antioxidant characteristics, like quercetin and rutin, have been found in *S. cumini* leaf **(Srivastava and Chandra, 2013)**.

5.3. Fruit of *Syzygium cumini*

A study suggested that the fruit of *S. cumini* is a source of natural antioxidants and has the ability to inhibit lipid peroxidation due to its content of tannins, vitamins, anthocyanins and phenolics **(Qamar et al., 2021)**. Fruits include a variety of bioactive substances including ascorbic acid, anthocyanins, flavonoids, tannins, total phenolics, and flavonoids **(Yanuarto and Nurani, 2022)**.

5.4. Biological Effects of *Syzygium cumini* Fruit

Different plant parts have been shown to have positive benefits in experimental in vivo and in vitro including antioxidant, anti-hyperlipidemic, and anti-hyperglycemic ones **(Ecker et al., 2017).** The active molecules of *S.cumini* support pharmacological effects in human health and metabolism including antioxidant, antibacterial, antidiabetic, central nervous system (CNS) activity, chemoprevention, anti-inflammatory, and anti-allergic properties **(Singh et al., 2019)**. Anti-inflammatory, anticancer, antidiabetic, antibacterial, antifungal, radioprotective, and antioxidant activities have all been noted by *S. cumini* **(Rehaman, 2021)**. *Syzygium cumini* plant is used as an antidiabetic agent **(Goyal, 2015).** Blackberries have been provided anti-inflammatory and antioxidant activities **(Chang et al., 2019)**. Research investigation by **Qamar et al., (2021)** has been confirmed the anti-inflammatory activity of S. cumini fruit extracts.

5.5. Antioxidant Effects of Syzygium *cumini* Fruit and its Mechanism for Protection against Oxidants

Antioxidants are essential compounds that can shield the organism from oxidative stress brought on by free radical damage **(Margaret et al., 2015)**. A study investigated that there is a relationship between the antioxidant capacities of various *S. cumini* plant sections and certain phenolic metabolites and other phenolic substances **(Halim et al., 2022)**. Because jambolan fruit naturally contains anthocyanin, it has strong antioxidant action **(Yanuarto and Nurani, 2022).** By several in vitro assays such as nitric oxide (NO), ferric-reducing antioxidant power (FRAP), oxygen radical absorbance capacity (ORAC) and 2,2-diphenyl-1-picrylhydrazyl (DPPH), the antioxidant activity of *S. cumini* has been proved **(Saeed et al., 2018).**

An investigation revealed that *S. cumini* fruit peels contain anthocyanins that cause protection against iron-induced lipid peroxidation **(Veigas et al., 2007)** and also contain tannins that have radical scavenging activities. With the increased concentration of tannins in *S. cumini* fruit extract, antioxidant and ferric-reducing power activity are increased **(Zhang and Lin, 2009)**. A study explored that anthocyanins present in *S. cumini* pulp exhibited strong radical-scavenging activity **(Sarma et al., 2020).** Fruit antioxidant activity is affected by several factors including genotype, growing temperature, growing season, maturity at harvest, and environmental stress **(Kupe et al., 2021).**

5.6. Mechanism of *S. cumini* for Protection against Different Oxidants

Exceeding the boundaries of antioxidant defense capabilities, oxidant chemicals' reactivity might set off chain reactions that disrupt the system. Exogenous antioxidants are required in order to neutralize the oxidants **(Yanuarto and Nurani, 2022).** Fruits, vegetables, and drinks contain antioxidants that are beneficial to human health in several ways, such as lowering the incidence of certain diseases and preventing cancer and cardiovascular disease. The primary kinds of antioxidants are supplements (vitamins; vitamins C and E), Carotenoids, polyphenols (flavonoids, flavonols, flavones, and flavanones), tannins, stilbenes, lignans, phenolic acids, anthocyanins, and isoflavones **(Oroian and Escriche, 2015).** An antioxidant is a substance that inhibits or delays the oxidation of a substrate in tiny concentrations. Antioxidant compounds work through a variety of chemical reactions to produce their effects, including single electron transfer (SET), hydrogen atom transfer (HAT), and the ability to bind transition metals **(Santos-Sánchez et al., 2019)**.

One can categorise antioxidants into two groups: primary and secondary. This classification is based on how antioxidants work. Primary antioxidants can transmit one electron through a single electron transfer mechanism or contribute an H-atom (hydrogen atom transfer, or HAT). These antioxidants are quite effective and are needed in small amounts to neutralize a huge amount of free radicals, these include phenolic antioxidants. Secondary antioxidants are defined as those that neutralise prooxidant catalysts. Examples include chelators of metal ions that are pro-oxidant (like Fe and Cu) **(Kumar et al., 2019)**.

The phenolic compounds have a crucial role in the signaling and defense mechanisms of plants. These substances work to reduce stress and have a variety of roles in plants. phenolic compounds have the ability to behave as hydrogen donors or to bind metal ions like iron and copper **(Paran et al., 2009).**In hydrogen atom transfer, a free radical interacts with an antioxidant with an H-atom. A neutral species is produced by stabilising the free radical that is transformed from an antioxidant to an antioxidant free radical **(Zeb, 2020).**

One of a phenolic compound's antioxidant functions is transition metal chelation (TMC). Studies have revealed that polyphenols bind transition metals to produce stable compounds **(Brown et al., 1998)**. Such processes can be catalyzed by transition metals like copper (Cu), manganese (Mg), and cobalt (Co). Food-derived phenolic compounds are excellent metalic chelators. Metalic chelation can prevent ferric reduction from happening directly, which in turn prevents the Fenton reaction from producing as many reactive OH-free radicals. The reduction capacities of the phenolic compounds determines the metal chelation **(Mathew et al., 2015)**.

The structure of phenolic compounds, including the benzene ring and the numbers and position of OH groups, determines their ability or potency to have the antioxidant effect. Antioxidant molecules are protected upon reacting with free radicals due to the benzene ring

(Rajan and Muraleedharan, 2017). It is important to note that another important consideration when determining the effectiveness of an antioxidant is the hydrogen atomic bond dissociation energy (BDE) bound to the phenolic oxygen atom (Leopoldini et al., 2011). Both flavonoids and phenolic acids are effective free radical scavengers. However, depending on their structural traits, variations may occur in the chelating opportunities with metals and reducing properties (Van Acker et al., 1996). Comparing flavonoids to phenolic acids, it has been found that the former has greater antioxidant activity (Zhang and Tsao, 2016). Quercetin, a flavonol with five hydroxyl groups, has a substantially higher antioxidant capacity than flavonols without free radical-neutralizing properties (TSAO, 2010).

5.7. Antioxidant Effects of *S. cumini* Fruit Extract Against Experimentally Induced Male and Female Reproductive Insult

A study proved that the jambul fruit pulp can revive germ cells and gradually restore spermatozoa's micrometric dimensions. Ingestion of jambul restores steroidogenesis and spermatogenesis in males after exposure to fluoride that impair these essential processes (Ahmad et al., 2012). Fruit of *S. cumini* has the ability to lower free radicals. In addition, there are more spermatocytes and there may be less spermatogenic cell death (Sukmaningsih et al., 2021).

6. Conclusion and Future Research

This review article concluded that cadmium is one of the most dangerous pollutants of environment that significantly affect both human and animal health. One of these cadmium-induced health hazards, is its reproductive toxicity. It induces its insult through generation of many reactive species such as superoxide anion, hydroxyl radicals, and hydrogen peroxide, which causes an increase in peroxidation of lipid, DNA alteration, and cell death. To alleviate its deleterious effects, an urgent need of intake of one of the medicinal plants that have antioxidant effects is uprising. *Syzygium cumini* is a promising candidate to achieve this goal. It has a variety of phytochemical compounds. These active compounds were observed to be present in different sections of the plant including leaves, seeds, peel, and pulp. These components make it one of the best medicinal plants that exert their antioxidant power against male and female reproductive injury induced by cadmium exposure. These valuable facts need to future research work to thorough the lights on the applicability of these antioxidant capacity of *Syzygium cumini* against cadmium induced toxicity of male and female reproductuive systems in lab animals.These research studies should concentrate on exploration of the biochemical and molecular mechanisms that will be done by this plant to mitigate cadminum induced toxicity.

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