**Nanobiotechnology: A tool to ameliorate the antidiabetogenic potential of *Syzygium cumini* (Jamun)**

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1. **Abstract**

The investigation by the researchers to design effective drug candidates by the use of natural compounds stood as our primary arsenal against a variety of chronic conditions. There has been a swift transformation in the evolution of botanical medicines and the issue of identification of new leads in the realm of chemical diversity extensive research on chemistry and clinical therapeutics has been carried out. This chapter fascinates the connection between *Syzygium cumini* (Jamun) and its green approach to synthesizing nanoparticles against anti-diabetic properties. Jamun, a traditional medicinal plant has various bioactive components like anthocyanins, polyphenols, and flavonoids that demonstrate its antidiabetogenic potential. However, challenges in determining the delivery and bioavailability have spurred the integration of nanotechnology. The green synthesized nanoparticles of Jamun are found to amplify the antidiabetogenic potential of its constituents. This holistic approach revolutionizes the treatment of diabetes offering more sustainable solutions to the diagnosed ones.

**Keywords:** *Syzygium cumini*, Green approach, Anthocyanins, Polyphenols, Flavonoids, Antidiabetogenic potential

1. **Introduction**

The world has been grappling with the menace of illness and there has been a consistent investigation by the researchers to design effective drug candidates to minimize the ill effects of medicines and improve their therapeutic properties. Throughout evolution, natural products have been bolstering our health, and treating diseases and injuries. The natural compounds stood as our primary arsenal against a variety of chronic conditions. Although there has been a wide use of plant-based medicines in the Orient as well as in the Occident, their exact nomenclature was unclear until the eighteenth and nineteenth centuries. The work of Serturner marked the beginning of natural product chemistry by isolating morphine from *Papaver somniferum*. The native people of the Andes and Amazon highlands used the bark of the cinchona tree as an infusion to treat fevers and by the early sixteenth century it was known as ‘Jesuit fever bark’ that brought a remarkable and profound change. Carl Koler, a German chemist isolated cocaine that could function as a local anesthetic in eye surgery. The alkaloid-rich oil extracted from *Pilocarpus jaborandi* served as a tool to combat glaucoma. The population of American Indians on the island of Guadeloupe cured stomach aches, and reduced inflammation in wounds by *Ananas comosos* [1]. Moreover, the twentieth century highlighted the discovery of several medicines as well as a large number of compounds, and their structures were identified that alleviated the significance of natural entities. The identification of molecular structures allowed scientists to synthesize rather than isolate these chemical species like emetine from *Cephaelis ipecacuanha*, quinine from *Cinchona ledgeriana*, atropine from *Atropa belladonna*, nicotine from *Nicotiana tobacum*, caffeine from *Coffea arabica* and others.

However, the actual medicinal properties of botanical remedies and their intricate blends’ composition remained unexamined and reflected their poor-quality control. Nonetheless, there has been a swift transformation in the evolution of botanical medicines due to several reasons such as the adverse effects of modern drugs, drug-resistant microorganisms, and others. Additionally, the concepts of traditional medicines have laid the foundation for the development of allopathy or modern drugs and the origin of new drugs by Newmann estimated that about 60% of the commonly used household names like reserpine, artemisinin, penicillin, paclitaxel are either directly or indirectly derived from plants.

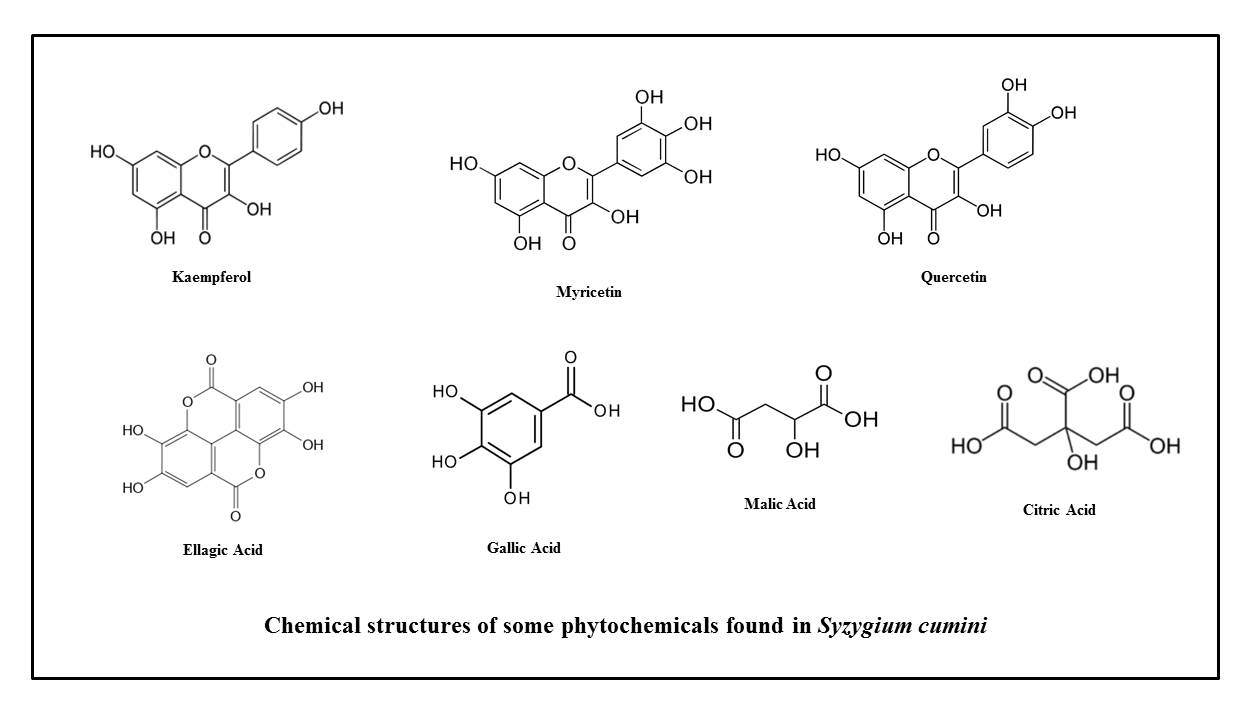
To resolve the issue of identification of new leads in the limited realm of chemical diversity extensive research on chemistry, pharmacology, clinical therapeutics, and pharmacognosy has been carried out on various medicinal plants. The utilization of combinatorial chemistry techniques to generate molecular diversity has been particularly valuable in testing numerous analogs of lead compounds to optimize their properties. Pharmaceutical industries aim to uncover the active agents that can aid in the development of novel drugs for ailments like cancer, malaria, diabetes, and many more.

According to information gained from the World Health Organization (WHO), nearly 80% of the global population is dependent on traditional medicines and among these 60% of the medicinal products available in the market are derived from natural sources found in plants [2]. The bioactive agents present in plant extracts possess therapeutic properties. These active agents such as flavonoids, alkaloids, phenylpropanoids, tannins, saponins, and terpenoids possess water solubility but exhibit limited absorption capabilities resulting in reduced bioavailability and subsequently impacting their therapeutic efficacy. The challenges of low bioavailability, unpredictable toxicity, reduced stability, and others are achieved by nanotechnology. The amalgamation of nanotechnology and medicinal plants offers a promising avenue to overcome the limitations through nano-encapsulation by encasing aromatic molecules within customized nanocarriers [3].

*Syzygium cumini*, commonly known as jamun or black plum is a herbal medicinal plant in the Unani system of medicine. Jamun is a versatile plant unveiling the presence of a range of vital compounds including alkaloids, flavonoids, steroids, cardiac glycosides, tannins, saponins, phenols, and terpenoids in its leaf extract [4]. The essential oils extracted from jamun leaves include transcaryophyllene (11.19%), α-caryophyllene (4.36%), α-pinene (32.32%), β- pinene (12.44%), 1,3,6- octatriene (8.41%), α-limonene (3.42%), and delta-3-carene (5.55%). These bioactive entities are responsible for its medicinal properties like anti-diabetic, anti-oxidant, anti-cancer, antiallergic, immunomodulatory, etc [5]. Not only the fruit of the jamun but also the extracts derived from its leaves, bark, and seeds have demonstrated effectiveness in diabetes treatment. Hence, jamun is a versatile fruit with various health conditions like regulating blood sugar levels, managing hyperglycemia and addressing associated health concerns.



Table 1: Showing phytochemicals and active constituents found in various plant parts of *Syzygium cumini*



1. **The Antidiabetogenic Effects of *Syzygium cumini* (Jamun)**

Anomalies in metabolism characterized by high blood sugar levels and decreased tolerance for glucose lead to the medical condition called Diabetes mellitus. Changes in the way hormones are controlled and impaired cellular processes contribute to the elevation of fasting blood glucose levels beyond 110mg/dL (6.1 mmol) and post-meal glucose levels exceeding 200mg/dL (11.1 mmol), thereby triggering the onset of Diabetes [6]. Individuals with diabetes often exhibit imbalances in the regulation of hormones, causing a surge in blood sugar levels and disrupting the body’s normal state of equilibrium. Diabetes primarily arises from pancreas dysfunction, which can hinder insulin secretion, disrupt insulin's normal function, or exhibit a combination of both, resulting in a diabetic condition.

Diabetes is primarily categorized into three main types: type 1, type 2, and gestational diabetes. Among these, type 2 diabetes constitutes the largest portion of diagnosed cases. Type 1 diabetes results from the body’s incapability to generate insulin, whereas type 2 diabetes arises when the body struggles to efficiently utilize insulin. Conversely, gestational diabetes refers to a situation where blood sugar levels are raised and this takes place while a woman is pregnant [7]. About 10.4% of the adult population in India is thought to experience diabetes, leading to a mortality rate of one million deaths [8]. At present, there exists a range of pharmaceutical drugs designed for the treatment of diabetes, including sulphonylureas, biguanides, alpha-glucosidase inhibitors, thiazolidinediones, and meglitinides. However, these medications come with diverse side effects such as hypoglycemia, weight gain, nausea, diarrhea, fluid retention, and abdominal bloating [9]. These complications underscore the necessity for novel antidiabetic medications with reduced side effects. Modern medicine offers a wide range of treatment strategies to effectively manage both Type 1 and type 2 diabetes. However, Ayurveda and nanotechnology offer extensive insights into the treatment of diabetes using Jamun. This review predominantly focuses on the therapeutic potential of Jamun, scientifically identified as *Syzygium cumini*, in the context of addressing Diabetes.

1. **Scavenging activity of Jamun**

The reduction ofblood sugar levels and the alleviation of hyperlipidemia by Jamun might not stem from a singular mechanism. Instead, multiple potential mechanisms appear to collaborate in a synchronized manner to manage diabetes and hyperlipidemia. Among these mechanisms, the combined effects of various factors seem to play a crucial role. The excess formation of free radicals/ reactive oxygen species (ROS) is one of the most important events in causing Diabetes [10,11]. Thus, the process of neutralizing these free radicals through the use of Jamun appears to play a pivotal role in the management of diabetes [12-14]. At the molecular level, the decrease in glucose levels can be attributed to Jamun's ability to activate PPARα, PPARγ, and AKT. This activation, in turn, leads to the downregulation of the expression of various molecules, including ACC1, Foxo-1, PGC1α, Scid 1, SREPB1c, endoplasmic reticulum protein retention receptor (KDEL), and GPR98. These downregulated molecules are responsible for the depletion of G6Pase, ADA, 5’NTase, PEPCK, and Fas activities [15-18], as shown in Figure 1.

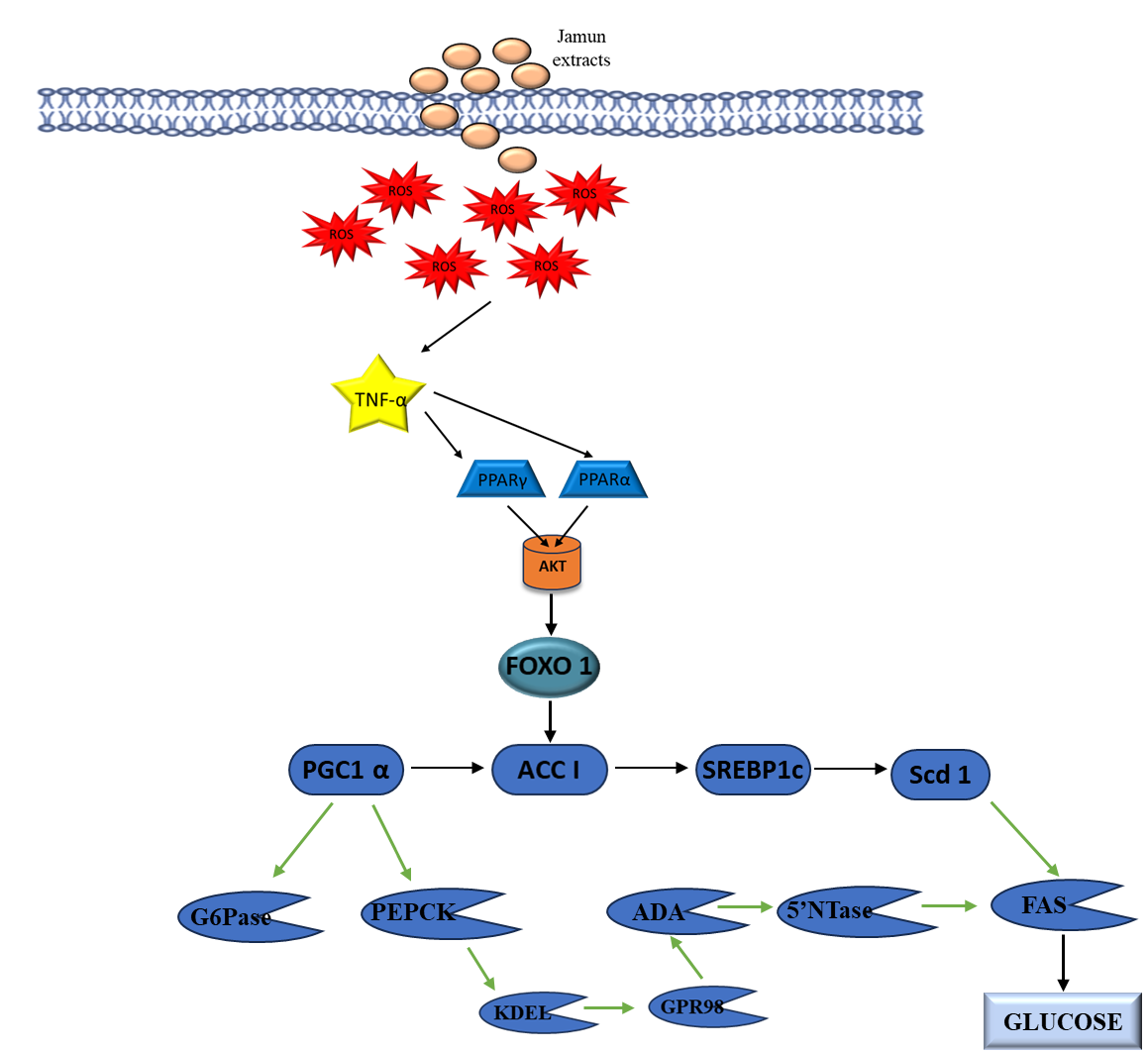


Figure 1(Cited from Ref. 37) Jamun fruit exhibits antioxidant properties by scavenging free radicals, which are reactive oxygen species (ROS). These ROS molecules play a role in modulating the expression of TNF-α and protein kinase (AKT). Furthermore, the fruit positively influences peroxisome proliferator-activated receptor gamma (PPARγ) and PPARα, leading to the downregulation of factors such as Forkhead box protein-1 (Foxo-1), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α), sterol regulatory element-binding protein-1c (SREBP1c), Acetyl-CoA carboxylase (ACC1), stearoyl-CoA desaturase-1 (SCD1), endoplasmic reticulum protein retention receptor (KDEL), G protein-coupled receptor (GPR98), fatty acid synthase (FAS), glucose 6-phosphatase (G6Pase), phosphoenolpyruvate carboxykinase (PEPCK), Adenosine deaminase (ADA), and 5’-nucleotidase (5’NTase).

1. **Mechanism of Action**

In Diabetes, there is a noted dysregulation of the Nrf2/Keap1/ARE (Antioxidant Response Element) signaling pathway [19]. Jamun appears to sequester Nrf2/Keap1 and facilitate the translocation of Nrf2 into the nucleus, effectively restoring this pathway to its normal functioning state. The activation of Nrf2 and its translocation into the nucleus triggers the activation of the Antioxidant Response Element (ARE). This, in turn, stimulates the production of heme oxygenase-1 (HO1) and NAD[P]H: quinone oxidoreductase-1 (NQO1). As a consequence, there is an increase in the levels of antioxidants, such as GPx, GSH, glutathione reductase (GR), SOD, catalase, and glutathione-s-transferase (GST) in diabetic conditions, resulting in a reduction of lipid peroxidation [20-22], as explained in Figure 2. In addition to these known mechanisms, Jamun may employ several other unidentified pathways to exert its antidiabetic effects.

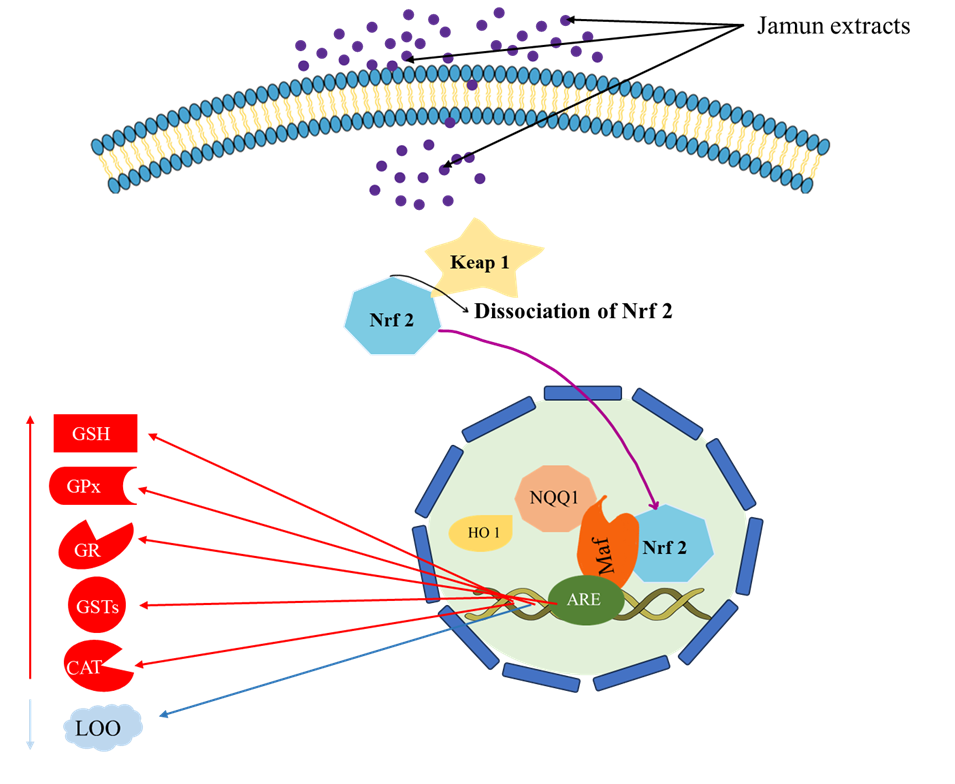


Figure 2 (Cited from Ref. 37) Jamun's efficacy in addressing diabetes stems from its capacity to disassociate nuclear factor E2-related factor 2 (Nrf2) from Keap1, resulting in the translocation of Nrf2 into the nucleus. Once localized in the nucleus, Nrf2 activates the antioxidant response element (ARE), consequently inducing the expression of heme oxygenase-1 (HO1) and NAD[P]H: quinone oxidoreductase-1 (NQO1). This cascade triggers an augmentation in the levels of glutathione (GSH), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione S-transferase (GST), and catalase (CAT), while concurrently diminishing lipid peroxidation (LOO).

Jamun contains anthocyanins that underlie its antidiabetic effects, however, various disadvantages like inadequate solubility, limited biological availability, instability, and unpredictable toxicity hinder their practical applications. To overcome these issues, nanotechnology plays a crucial role in unlocking their full potential for use in pharmaceutical formulations. The convergence of nanotechnology and combinatorial chemistry presents a promising avenue to enhance the efficacy of Jamun’s antidiabetic potential. This method provides a fundamental understanding of the principles employed in designing, characterizing, producing, and applying materials on a nanoscale. As a result, it deals with the constraints linked to anthocyanins.

1. **Green Synthesis of nanoparticles by using *Syzygium cumini*** **(Jamun)**

In the context of eco-friendly nanoparticle synthesis, various compounds including vitamins, microorganisms, sugars, biopolymers, and plant extracts, find applications as both capping and reducing agents. Notably, recent advances have enabled the creation of nanoparticles through the utilization of plant components like tissues and extracts [23]. Among the available methods, plant-based extracts emerge as particularly well-suited for large-scale, environmentally conscious nanoparticle synthesis.

For instance, the Jamun plant, known for its rich content of beneficial compounds, could play a significant role in this approach. Jamun plants possess molecules such as phenols, nitrogen compounds, terpenoids, and other antioxidants that effectively scavenge free radicals [27]. The presence of phytosterols and polyphenols within these plants further enhances their suitability for application in nanoparticle synthesis.

1. **Different types of nanoparticles synthesized from *Syzygium cumini***

* **Silver nanoparticles**

Polar-soluble components play a pivotal role in the synthesis of silver nanoparticles (SNP). Researchers have observed a direct connection between the number of polyphenols and surfactants within the reaction solution and the size of the generated SNP. As a result, the quantity of polyphenols emerges as a potentially critical factor influencing both the size and distribution characteristics of the resulting silver nanoparticles [32]. The authors also reported the spherical agglomerated silver nanoparticles of the leaf and seed extract as confirmed by SEM and atomic force microscopy (AFM). Figure 3 shows the morphology and microscopy results of the synthesized silver nanoparticles. The average size of Ag nanoparticles synthesized by leaf extract, leaf water fraction, seed extract, and seed water fraction were 30,29,92, and 73 nm respectively, as shown in Figure 4.

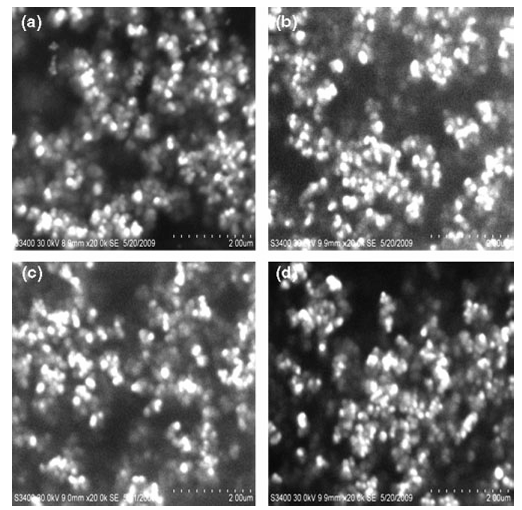


Figure 3. SEM images of SNP synthesized with (a) leaf extract, (b) leaf water fraction, (c) seed extract, and (d) seed water fractions of *S.cumini*. Adapted from [27]

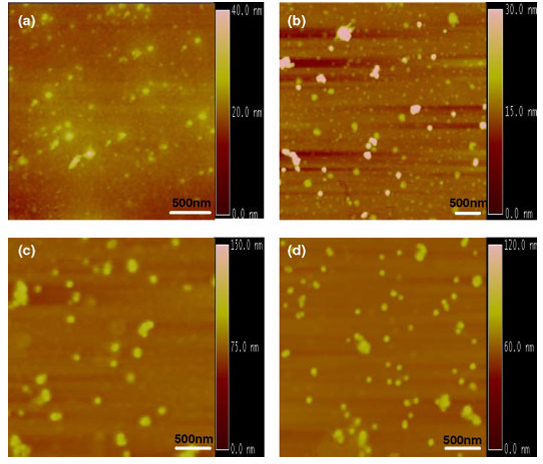


Figure 4. Tapping mode AFM images of SNP synthesized with (a)leaf extract (LE), (b) leaf water fraction, (c) seed extract (SE), (d) seed water fractions of S. cumini. A scale bar of 500 nm is labeled in each image. Adapted from [27]

* **Polymeric Nanoparticles**

Paula et. al. [29] conducted an antidiabetic study comparing Jamun seeds and Janum-mediated polymeric nanoparticles. They showcased how polymeric nanoparticles carrying an aqueous extract of *Syzygium cumini* (Jamun) not only preserved the extract's antioxidant properties but also elevated its antifungal efficacy *in vitro* [28]. Significantly, these polymeric nanoparticles emerged as a valuable alternative due to their adeptness in controlling drug release. Their attributes include bio-compatibility, biodegradability, and superior stability in comparison to other systems. Moreover, they also proved that nanoparticles containing the aqueous extract of *S. cumini* are more effective than the aqueous extract of *S. cumini* in reducing glucose (56%), cholesterol (33%), and creatinine (51%) levels. The polymeric nanoparticles also exhibited a substantial impact on serum (16%) and pancreatic (46%) AOPP levels, as well as renal (48%) TBARS levels when compared with the DMþC (diabetes mellitus plus C. albicans) group, as depicted in Figure 5. In the context of the C. albicans group, both treatments led to a decrease in NAG activity, but no reduction in creatinine levels was observed.

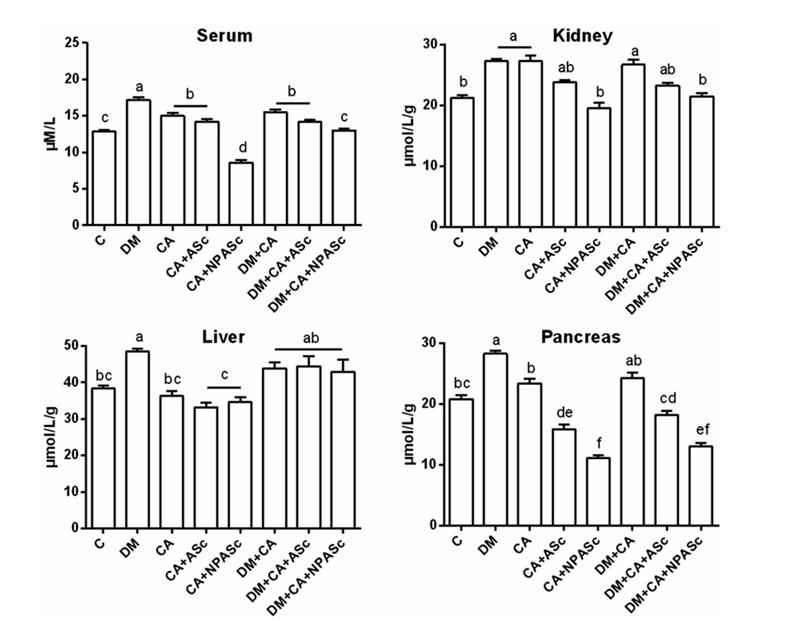


Figure 5. Impact of jamun seed extract and seed extract loaded polymeric nanoparticle treatments on AOPP levels in the serum (μM/L) and tissue (μmol/L/g of protein) of rats. The data is presented as the mean ± SEM (n=6). Significantly different mean values are denoted by distinct letters (p<0.05) according to the Duncan test. The experimental groups include: DM - diabetic rats; CA - rats infected with Candida albicans; CA+ seed extract - rats infected with Candida albicans and subjected to seed extract treatment; CA + seed extract loaded polymeric nanoparticle - rats infected with Candida albicans and treated with NP; DM+CA - diabetic rats infected with Candida albicans; DM +CA +seed extract - diabetic rats with Candida albicans infection and seed extract treatment; DM+CA+NP- diabetic rats with Candida albicans infection and NP treatment. Adapted from [29]

* **ZnO Nanoparticles**

Daniel and coworkers in 2019 [30] synthesized and assessed the antidiabetic impact of Zinc oxide nanoparticles derived from *Syzygium cumini*. Their findings indicated that the acquired ZnO nanoparticles achieved stabilization through interactions with phenolic compounds present in the seed extract, as indicated by FT‑IR analysis. Moreover, the XRD pattern analysis verified the crystalline nature of the nanoparticles, shown in Figure 6 (a) and (b) while TEM images unveiled their polygonal structure with dimensions ranging from 16.7 to 22.9 nm, as shown in Figure 7

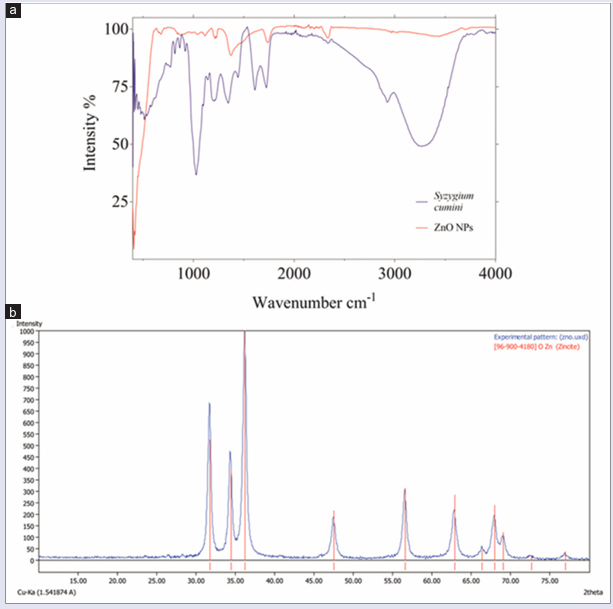


Figure 6. Spectral characterization of zinc oxide nanoparticles (a) Fourier transform-infrared chromatogram of zinc oxide nanoparticles and Syzygium cumini seed extract and (b) X-ray diffraction spectra showing the diffraction pattern of the synthesized zinc oxide nanoparticles. Adapted from [30]

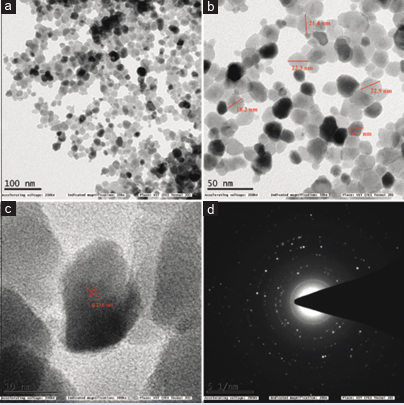


Figure 7. Transmission electron microscopy analysis of the synthesized zinc oxide nanoparticles, (a and b) Morphology and size (c) d-spacing of the surface and (d) Selected area electron diffraction. Adapted from [30]

In-depth molecular interaction investigations between the phenolic compounds extracted from the *Syzygium cumini* seeds and α‑amylase and α‑glucosidase revealed a pronounced affinity toward these enzymes, surpassing that of acarbose, as shown in Figure 8.

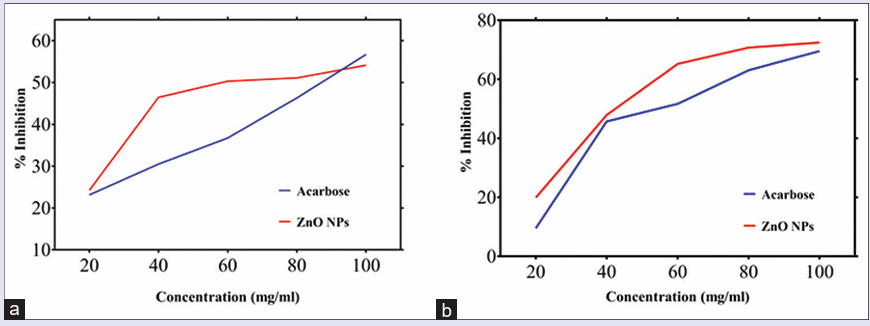


Figure 8. Inhibitory potential of zinc oxide nanoparticles and acarbose against (a) α-amylase and (b) α-glucosidase Adapted from [30]

Additionally, the in vitro inhibitory potential studies of the ZnO nanoparticles demonstrated their capacity to inhibit enzymes similar to acarbose. Studies have indicated that metal oxide nanoparticles have the ability to penetrate the plant cell wall, concurrently elevating the levels of ROS, RNS, and chlorophyll content [34]. In a separate investigation conducted by Daniel et al. in 2020 [26], the size of the Zinc oxide nanoparticles (ZnO NPs) produced using jamun-mediated synthesis was determined to be 18.92 nm. Notably, through in vitro studies conducted on rat insulinoma (RIN-5F) cells, it became evident that cells treated with the synthesized ZnO NPs displayed a dose-dependent increase in insulin secretion. Furthermore, when administered to streptozotocin-fructose-induced type II diabetic rats, the ZnO nanoparticles showcased significant effects. This encompassed a substantial reduction (p < 0.01) in blood glucose levels, as well as marked decreases in total cholesterol, triglycerides, and low-density lipoprotein levels. Conversely, there was a noticeable increase (p < 0.01) in serum insulin levels and liver antioxidant enzyme levels. These combined findings underscored the nanoparticles' role as both a hypoglycemic and hypolipidemic agent.

Furthermore, the treatment of ZnO NPs in diabetic rats yielded an augmented number of beta cells, attributed to the heightened insulin levels and reduced glucose levels. In conclusion, the synthesized ZnO NPs demonstrated a compelling hypoglycemic effect in diabetic rats, thereby highlighting their potential as a potent antidiabetic medication. A significant revelation from the study revealed that ZnO nanoparticles (NPs) induced nuclear damage and brought about modifications at the cellular level in the A549 human lung cancer cell line, with the extent of these effects being dependent on the concentration of the nanoparticles. In a separate experiment, ZnO NPs synthesized through a green method, were employed as a nutritional source for cultivating sesame plants at various concentrations (1,3,5,7,9 mg/ml). Collectively, the research underscored the role of ZnO nanoparticles in both nanomedicine and nano-nutrient applications [33]. These findings indicate that nanotechnology has the potential to enhance the beneficial characteristics of plant extracts, like their antioxidant activity, which could have practical applications in addressing complications related to diabetes.

Table 2: Nanoparticles synthesized from different parts of *Syzygium cumini*



1. **Future Perspective**

Recent research advances have highlighted the broad spectrum of applications for plant-derived nanoparticles in the regulation of disorders and diseases driven by oxidative stress. Accumulating evidence from published literature strongly indicates that plant-derived nanoparticles hold significant promise as innovative and potent therapeutic agents for addressing conditions stemming from oxidative stress-induced damage. Moreover, green synthesis of nanoparticles exhibits a versatile range of medicinal utilities encompassing antioxidative properties, as well as displaying capabilities as antidiabetic, antibacterial, antifungal, anticancer, and antiplasmodial agents. Notably, they manifest the capacity to catalytically modulate biomolecular reactions with redox attributes. While these attributes hold significant promise, it is imperative to channel further research efforts towards addressing key challenges inherent in the synthesis and practical integration of plant-derived within pharmacological contexts. The green synthesis of nanoparticles involves the utilization of metals, which could potentially pose toxicity risks when consumed in significant amounts by humans. A considerable number of reports lack essential information regarding the toxicity profile of the produced nanoparticles, as well as pertinent biological investigations. In order to tackle these concerns encompassing the exact mechanisms, distribution, toxicity, and potential negative impacts, it is imperative to conduct thorough and extensive pharmacokinetic studies.

1. **Conclusion**

Natural products are considered to be extremely valuable encompassing both straightforward and exceedingly intricate chemical structures. The natural metabolites are superior in terms of biochemical and pharmacological activities and the drug discovery process from natural products is associated with isolation, purification, screening, and drug discovery of novel drug candidates. Therefore, the blend of nanotechnology and plant-derived medicinal products represents a promising avenue in pharmaceutical research. By encapsulating or modifying these products at the nanoscale, their bioavailability and therapeutic potential can be significantly improved, leading to more effective treatments and reduced side effects. This interdisciplinary approach leverages the wisdom of traditional medicine and demands careful consideration of safety, regulatory compliance, and ethical implications to ensure that the resulting therapies are both effective and responsible.

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