

NANOBIOTECHNOLOGY: A TOOL TO AMELIORATE THE ANTIDIABETOGENIC POTENTIAL OF SYZYGIUM CUMINI (JAMUN)

Abstract

Researchers have been investigating the design of effective drug candidates using natural compounds as our primary strategy against various chronic conditions. Diabetes mellitus, a complex metabolic disorder imposing a substantial global health burden, has driven the search for innovative solutions. This quest has led to the exploration of nanobiotechnology as a transformative tool to harness the antidiabetic potential of natural compounds, with a particular focus on *Syzygium cumini*, commonly known as Jamun. Jamun, a traditional medicinal plant, harbors various bioactive components such as anthocyanins, polyphenols, and flavonoids, showcasing significant antidiabetogenic potential. The unique properties of black plum such as insulin-mimetic effects, α -glucosidase inhibition, and enhanced insulin secretion from pancreatic β - cells make it a natural and safe remedy for diabetes management. This chapter explores the fascinating connection between *Syzygium cumini* (Jamun) and its eco-friendly approach to synthesizing nanoparticles with anti-diabetic properties. However, challenges related to delivery and bioavailability have spurred the integration of nanotechnology. The green-synthesized nanoparticles derived from Jamun have demonstrated the capability to amplify the antidiabetogenic potential of their constituents. Integrating nanobiotechnology into the *Syzygium cumini* (Jamun) study presents a promising avenue for improving diabetes management. This interdisciplinary approach effectively bridges the gap between traditional herbal medicine and cutting-edge nanotechnology, providing efficient, targeted, and sustainable solutions for

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Diabetes. As research in this field continues to advance, the collaboration between natural remedies and modern technology holds the potential to alleviate the global burden of Diabetes, instilling hope for improved health outcomes among individuals affected by this chronic condition.

Keywords: Diabetes mellitus, Syzygium cumini, Nanobiotechnology, Green-synthesized nanoparticles, Anthocyanins, Polyphenols, Flavonoids, Antidiabetogenic potential

I. INTRODUCTION

The world has been grappling with the menace of illness, and researchers have consistently investigated 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 served as our primary arsenal against various chronic conditions. Although plant-based medicines have been widely used in the Orient and the Occident, their exact nomenclature was still being determined in the eighteenth and nineteenth centuries. The work of Serturmer 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. It was known as 'Jesuit fever bark' by the early sixteenth century, which 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 comosus* [1]. Moreover, the twentieth century highlighted the discovery of several medicines and many 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, and paclitaxel are either directly or indirectly derived from plants. To resolve the issue of identifying 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. Using combinatorial chemistry techniques to generate molecular diversity has been particularly valuable in testing numerous analogs of lead compounds to optimize their properties. The pharmaceutical industries aim to uncover active agents that can aid in developing 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. Approximately 60% of the pharmaceuticals currently on the market are sourced from natural compounds 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. Nanotechnology has overcome the challenges of low bioavailability, unpredictable toxicity,

reduced stability, and others. 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 anherbal medicinal plant in the Unani system of medicine. Jamun is a versatile plant unveiling the presence of a range of vital compounds in its leaf extracts, including alkaloids, flavonoids, steroids, cardiac glycosides, tannins, saponins, phenols, and terpenoids [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 their medicinal properties like antidiabetic, antioxidant, anticancer, 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 [37]. Hence, Jamun is a versatile fruit with various health conditions, like regulating blood sugar levels, managing hyperglycemia, and addressing associated health concerns. The following **Table 1** depicts the phytochemicals and active constituents found in the plant parts of black plum.

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

S. No.	Plant part	Phytochemicals	Active Constituents
1.	Leaves	Mycaminose, crategolic (Maslinic) acid, β -sitosterol, Betulinic acid, heptacosane, n-dotricontanol, quercetin, n-nonacosane, n-hentriacontane, n-octacosanol, ntriacontanol,myricetin, myricitrin and the flavonols glycosides myricetin 3-O- (400-acetyl)- α L-rhamnopyranosides.	Ferrullic acid, catechin, cretegolic acid, n-dotricontanol, myrcetin, mycaminose, quercetin, tannic acid, BHA, Tocopherol.
2.	Flower	Oleanolic acid, Ellagic acids, isoquercetin, quercetin, Kaempferol, and myricetin.	Erategolic acid, isoquercetin, quercetin, Kaempferol Oleanolic acid.
3.	Fruit Pulp	Anthocyanins, delphinidin, petunidin, malvidin-diglucosides.	Petunidin, α -pinene, β - pinene, malvidin, peonidin, 60yaniding, delphinidin, pelargonidin.
4.	Seeds	Jambosine, gallic acid, ellagic acid, corilagin, 3,6-hexahydroxydiphenoylglucose, 1-galloylglucose, 3-galloylglucose, quercetin, β -sitosterol, 4,6 hexahydroxy diphenoylglucose	Quercetin, Rutin, 3,5,7,4-tetrahydroxy flavones, caffeic acid, ellagic acid, ferullic acid, albumen, fat, jambosine, ellagic acid, lauric, myristic, palmitic, stearic, oleic acid, linoleic,

			malvalic and vernolic acid and phytosterols such as β -sitosterol.
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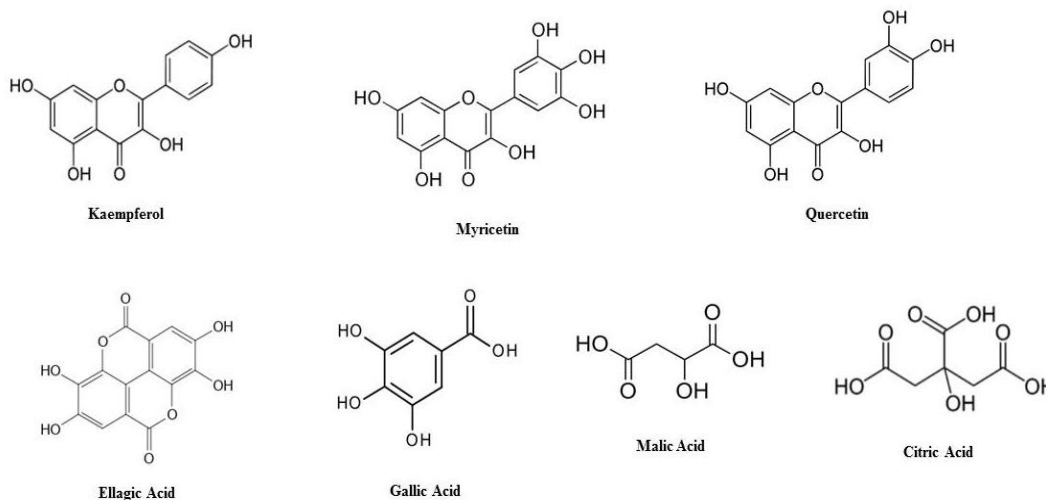


Figure 1: Shows some of the chemical structures of phytoconstituents found in various plant parts of *Syzygiumcumini*.

II. 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 categorized into three main types: type 1, 2, and gestational Diabetes. Among these, type 2 diabetes constitutes the most significant portion of diagnosed cases. Type 1 diabetes results from the body's inability to generate insulin, whereas type 2 diabetes arises when the body struggles to utilize insulin efficiently. 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]. Currently, a range of pharmaceutical drugs are designed for treating 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 fewer 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 treating Diabetes using Jamun. This chapter predominantly focuses on the therapeutic potential of Jamun, scientifically identified as *Syzygium cumini*, in the context of addressing Diabetes.

1. The scavenging Activity of Jamun: The reduction of blood 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 play a crucial role. The excess formation of free radicals and reactive oxygen species (ROS) is one of the most critical 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 managing diabetes [12-14]. At the molecular level, the decrease in glucose levels can be attributed to Jamun's ability to activate PPAR α , PPAR γ , and AKT. This activation, in turn, leads to the downregulation of the expression of various molecules, including ACC1, Foxo-1, PGC1 α , Scd 1, SREBP1c, 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 2.

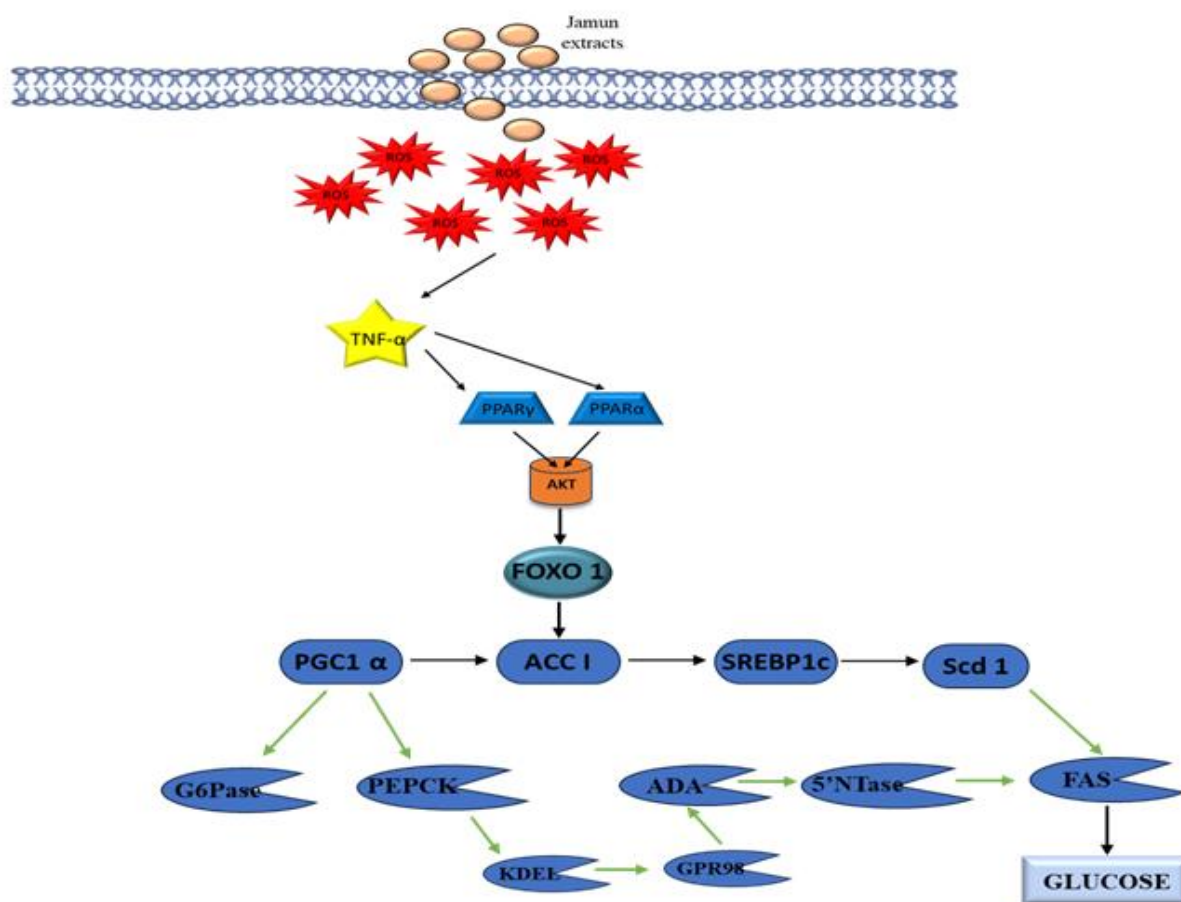


Figure 2: (Cited from Ref. 36) Jamun fruit exhibits antioxidant properties by scavenging free radicals, which are reactive oxygen species (ROS). These ROS molecules play a role in modulating the expression of TNF- α and protein kinase (AKT). Furthermore, the fruit positively influences peroxisome proliferator-activated receptor gamma (PPAR γ) and PPAR α , leading to the downregulation of factors such as Forkhead box protein-1 (Foxo-1), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1 α), 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).

2. 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 trigger 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 3. In addition to these known mechanisms, Jamun may employ several other unidentified pathways to exert its antidiabetic effects.

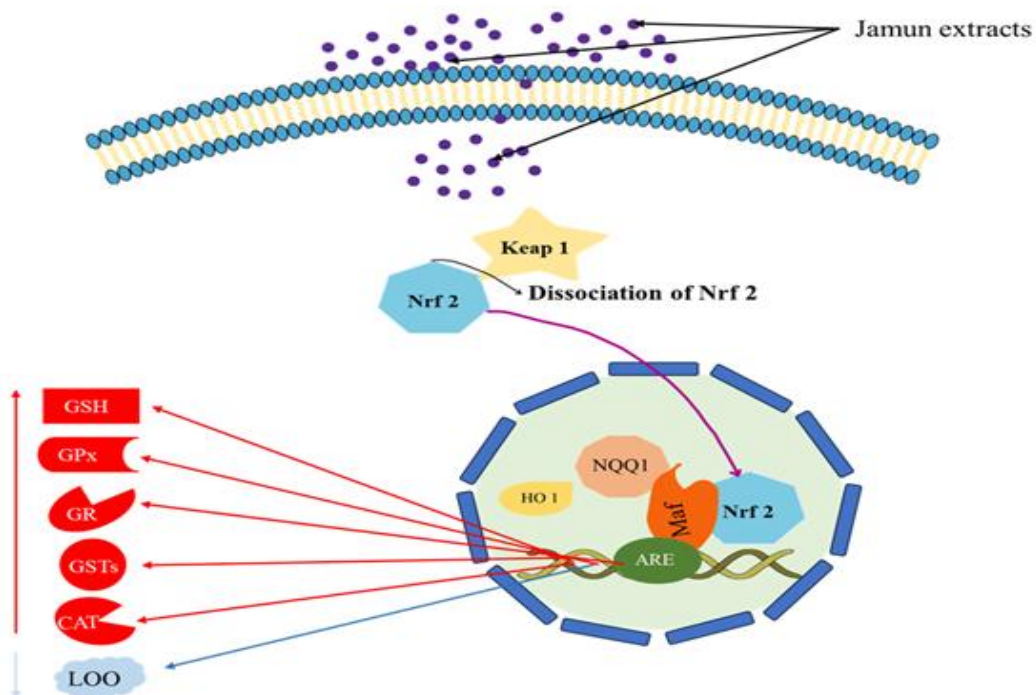


Figure 3: (Cited from Ref. 36) Jamun's efficacy in addressing Diabetes stems from its capacity to disassociate nuclear factor E2-related factor 2 (Nrf2) from Keap1,

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 is crucial in unlocking their full potential for use in pharmaceutical formulations. The convergence of nanotechnology and combinatorial chemistry presents a promising avenue to enhance 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.

III. 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 are 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 [18]. The presence of phytosterols and polyphenols within these plants further enhances their suitability for application in nanoparticle synthesis.

Different types of nanoparticles synthesized from *Syzygium cumini*

- 1. Silver nanoparticles:** Polar-soluble components play a pivotal role in synthesizing 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 the resulting silver nanoparticles' size and distribution characteristics [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 4 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 was 30,29,92, and 73 nm, respectively, as shown in Figure 5.

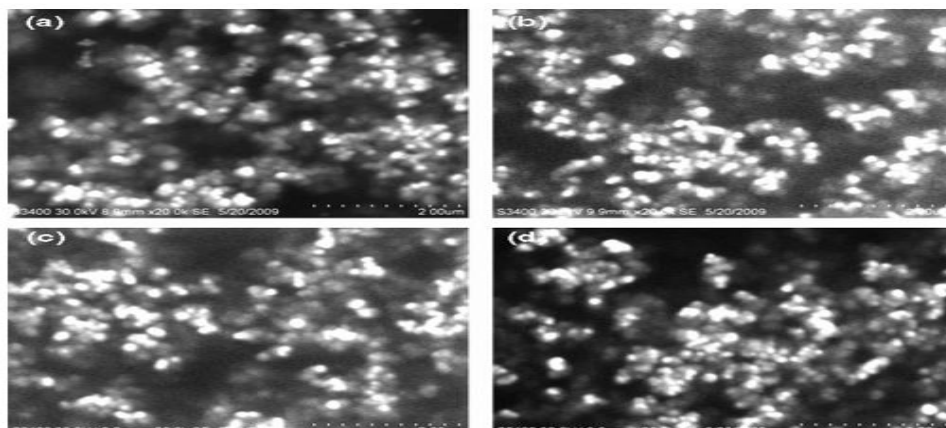


Figure 4: SEM images of SNP synthesized with (a) leaf extract, (b) leaf water fraction, (c) seed extract, and (d) seed water fractions of *S.cumini*. Adapted from [18]

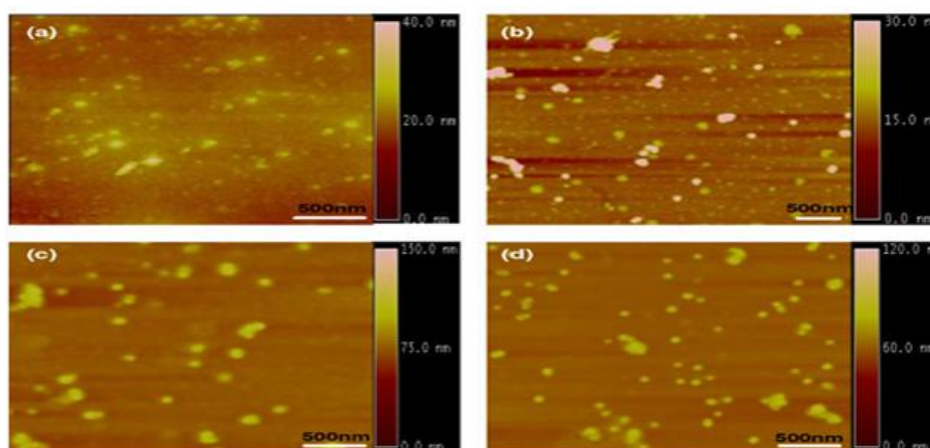


Figure 5: Tapping mode AFM images of SNP synthesized with (a) leaf extract (LE), (b) leaf water fraction, (c) seed extract (SE), and (d) seed water fractions of *S. cumini*. A scale bar of 500 nm is labelled in each image. Adapted from [18]

- 2. Polymeric Nanoparticles:** Paula et al. [28] 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) preserved the extract's antioxidant properties and elevated its antifungal efficacy in vitro [27]. Significantly, these polymeric nanoparticles emerged as a valuable alternative due to their adeptness in controlling drug release. Their attributes include biocompatibility, biodegradability, and superior stability compared 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%). 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 DMpC (diabetes mellitus plus *C. albicans*) group, as depicted in Figure 6. In the context of the *C. albicans* group, both treatments decreased NAG activity, but no reduction in creatinine levels was observed.

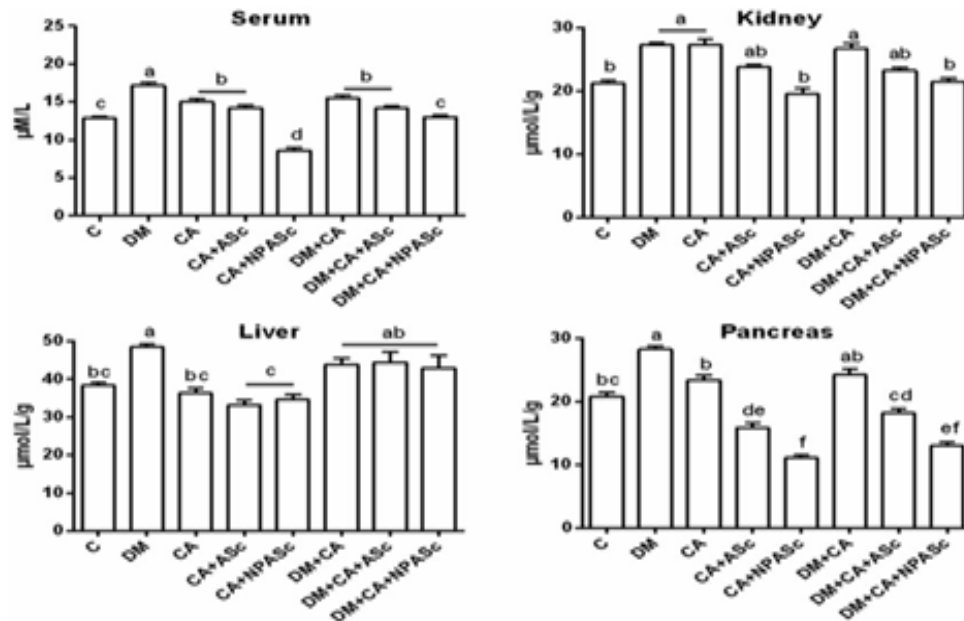


Figure 6: Impact of jamun seed extract and seed extract loaded polymeric nanoparticle treatments on AOPP levels in the serum ($\mu\text{M/L}$) and tissue ($\mu\text{mol/L/g}$ of protein) of rats. The data is presented as the mean \pm SEM ($n=6$). Significantly different mean values are denoted by distinct 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 [28]

- ZnO Nanoparticles:** Daniel and coworkers in 2019 [29] synthesized and assessed the antidiabetic impact of Zinc oxide nanoparticles derived from *Syzygium cumini*. Their findings indicated that the acquired ZnO nanoparticles stabilized through interactions with phenolic compounds 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 7(a) and (b), while TEM images unveiled their polygonal structure with dimensions ranging from 16.7 to 22.9 nm, as shown in Figure 8.

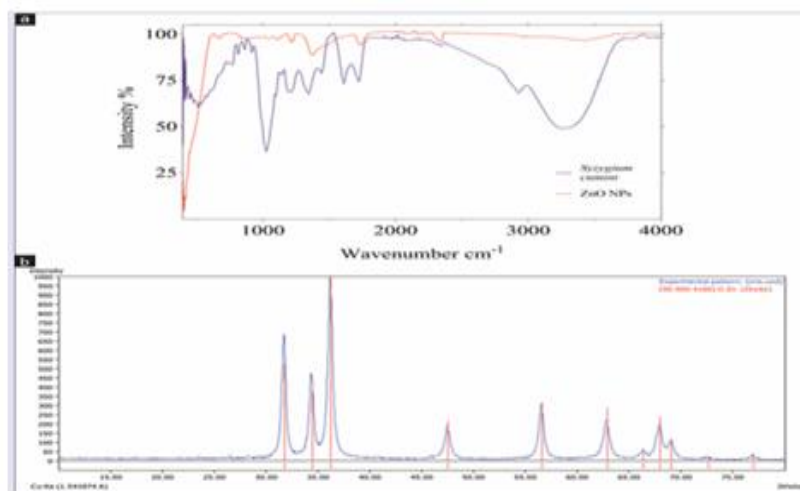


Figure 7: Spectral characterization of zinc oxide nanoparticles (a) Fourier transform-infrared chromatogram of zinc oxide nanoparticles and Syzygium cumini seed extract and (b) X-ray diffraction spectra showing the diffraction pattern of the synthesized zinc oxide nanoparticles. Adapted from [29]

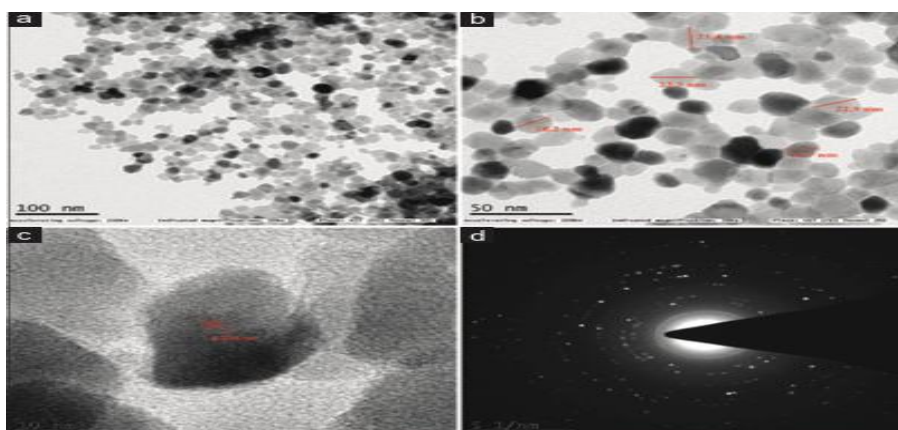


Figure 8: Transmission electron microscopy analysis of the synthesized zinc oxide nanoparticles, (a and b) Morphology and size, (c) d-spacing of the surface and (d) Selected area electron diffraction. Adapted from [29]

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 9.

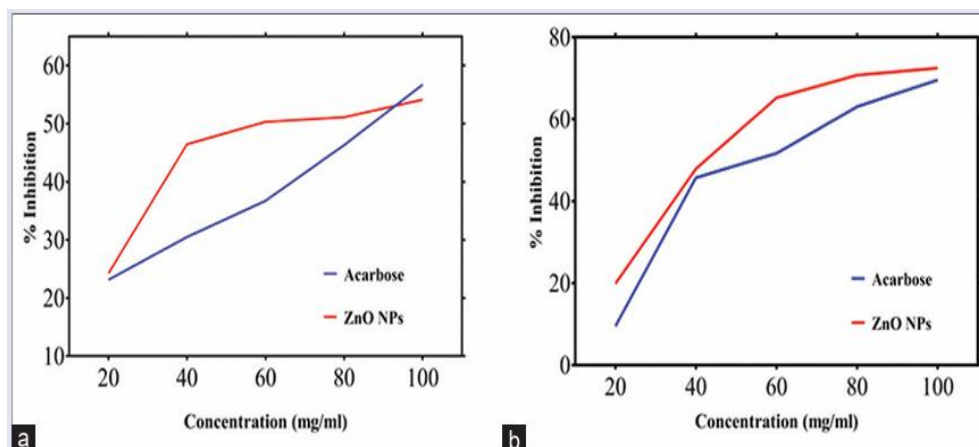


Figure 9: Inhibitory potential of zinc oxide nanoparticles and acarbose against (a) α -amylase and (b) α -glucosidase Adapted from [29]

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 can penetrate the plant cell wall, concurrently elevating ROS, RNS, and chlorophyll levels [33]. 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, *in vitro* studies conducted on rat insulinoma (RIN-5F) cells showed 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 and 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 hypoglycemic and hypolipidemic agents.

Furthermore, treating 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 NPssynthesized through a green method were employed as a nutritional source for cultivating sesame plants at various concentrations (1,3,5,7,9 mg/ml). The research underscored the role of ZnO nanoparticles in nanomedicine and nano-nutrient applications [32]. 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. The nanoparticles synthesized from different parts of jamun with their size, and shape using the green approach have been mentioned in Table 2

Table2: Nanoparticles synthesized from different parts of Syzygium cumini

Plant Part	Nanoparticle	Size(Nm)	Shape	References
SEEDS	ZnO	16.7–22.9 nm	Polygonal	[29]
LEAVES	ZnO	11.35 nm	Hexagonal	[34]
LEAVES	α -Fe ₂ O ₃	NA	Irregular spherical shaped	[35]
SEEDS	ZnO	18.92 nm	Hexagonal	[30]
SEEDS	Ag	92 nm	Spherical	[31]
LEAVES	Ag	30 nm	Spherical	[31]

IV. FUTURE PERSPECTIVE

Recent research advances have highlighted the broad spectrum of applications for plant-derived nanoparticles in regulating 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 and displaying capabilities as antidiabetic, antibacterial, antifungal, anticancer, and antiplasmodial agents. Notably, they can catalytically modulate biomolecular reactions with redox attributes. While these attributes hold significant promise, it is imperative to channel further research efforts toward addressing key challenges inherent in the synthesis and practical integration of plant-derived compounds within pharmacological contexts. The green synthesis of nanoparticles involves the utilization of metals, which pose toxicity risks when consumed in significant amounts by humans. Many reports need more essential information regarding the toxicity profile of the produced nanoparticles and pertinent biological investigations. To tackle these concerns, which encompass the exact mechanisms, distribution, toxicity, and potential negative impacts, it is imperative to conduct thorough and extensive pharmacokinetic studies.

V. 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 the 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. It demands careful consideration of safety, regulatory compliance, and ethical implications to ensure that the resulting therapies are both practical and responsible.

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