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MEDICINAL EFFICACY OF EDIBLE MACRO FUNGUS *Ganoderma applanatum* (PERS.) PAT. – A REVIEW

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ABSTRACT
Medicinal mushrooms are used in traditional medication. They are easily available and cost effective source for the people of rural and tribal areas. In the present review, an attempt has been made to congregate the taxonomic, mycochemical and pharmacological studies done on an important medicinal mushroom*Ganoderma applanatum*. Extensive experimental studies prove that *Ganoderma applanatum* possesses antibacterial, antifungal, antiviral, antioxidant, anticancer, anticholestromic, antidiabetic, nephroprotective, hepatoprotective, hypouricemic, immunostimulatory properties, which help it to play role in prevention and treatment of many disease. Therefore, it is worthwhile to review therapeutic properties of *G. applanatum* to give an overview of its status to scientist both modern and ancient.

INTRODUCTION

Improper nutrition and modern lifestyle are the two common reasons for the growth of diseases and disorders all over the world (Kozarski *et al.,* 2015).It has been estimated by the World Health Organization (WHO) that about 80% of the earth's inhabitants rely on traditional medicine for their primary health care (Krishnaiah *et al.,* 2011). Since beginning of mankind nature is the most important source of medicines, and the bioactive compounds produced from traditionally used living organisms have been used directly as drugs or as lead compounds for drug development.Medicinal mushrooms have the potentiality to become real drugs of traditional and evidence-based medicine (Lindequist *et al.,* 2014).

The mushrooms have been defined as a potential source of dietary fiber, high quality of proteins, essential amino acids, as well as the numerous vitamins and minerals, polysaccharides, glycoproteins, unsaturated fatty acids, phenolic compounds, ergosterols, lectins *etc.* (Gaoxing *et al.,*2018). In recent years innumerable studies have been focusing on the therapeutic benefits of mushrooms,including the immune boosting activity, anticancer, anti-inflammatory, antioxidant, antifungal, antibacterial, antiviral and many other medicinal properties (Rathore *et al.,* 2017; Gaoxing *et al.,* 2018).

It is estimated that nearly 1,40,000 mushroom species are found all over the world and among them only 5 percent could profit the mankind. Most edible and certain non-edible, non-consumptions mushrooms have been recognized to improve health from several thousand years ago (Bell *et al.,*2022).Traditional mycological knowledge of most Indian ethnic groups has proven to be extensive and profound, consuming nearly 283 species of wild mushrooms as food and medicine out of the 2,000 species (Choudhary *et al.,*2015).

Mushrooms belonging to genus *Ganoderma,* commonly known as Reishi mushrooms, is the largest genus in the order Polyporales with more than 400 records, are known for their medicinal importance in the Asian continent. Boundless traditional medicinal uses of *Ganoderma* species have attracted the pharmaceutical industry recently (Loyd *et al*., 2018). Several studies reported that *Ganoderma applanatum* has many medicinal properties such as antibacterial, antiviral, antitumor, antifibrotic, antiobesity, antioxidative, and immunomodulatory (Luo *et al.*, 2017 Gao *et al.*, 2019). The goal of the present review is therefore to crystalize the knowledge of the effectiveness of *Ganoderma applanatum* as a possible natural oral hypoglycemic, hypolipidemic, and hepatoprotective agent, or functional food, in reducing hyperglycemia along with other vascular complications reported by different workers apart from other aspects of medicinal efficacy of the species.*Ganoderma* mushrooms are important medicinal mushroom, being used in clinical, pharmaceutical, and nutritional industries for the treatment of various diseases such as migraine, hypertension, asthma, hepatitis, cancer, and cardiovascular problems (Mawar *et al.,*2020).

This review covers bioactivities of medicinal mushroom *Ganoderma applanatum* from different countries of the world. In this context, we aimed to give an overview and summarization of the nutritional, therapeutic benefits and other bioactivities of *G. applanatum* in the present review. The

review including the bioactive nutraceuticals in *G. applanatum* and their functioning mechanisms, which could be conducive to the better understanding of the correlations between the *G. applanatum* consumption and health improvement.

Taxonomic and medicinal history

The genus *Ganoderma* was established as genus in 1881 with with single species *G. lucidum* (Curtis:Fr.) P. Karst from England as the type species by Finnish mycologist Peter Adolf Karsten and before Karsten this taxon was characterized as *Boletus lucidum* by Curtis in 1781 (Karsten, 1881; Palanna *et al.,*2020). The mushroom *G. applanatum* was first reported by German mycologist Christiaan Hendrik Persoon who made additions to Linnaeus mushroom taxonomy. He gave it the binomial scientific name *Boletus applanatus* and this polypore was transferred to genus *Ganoderma* in 1887 by the French mycologist Narcisse Theophilr Patouillard (First Nature, 2021).

From ancient time the mushroom of genus *Ganoderma* has been used as traditional medicinal supplement in some Asian countries such as China, Japan and India.The main product is the dried fruit body of *G. applanatum* used as traditional Chinese medicine and it has also been reported as a medicinal farming crop and is used as a flavor enhancer in Asian cuisine because of its rich mushroom flavor. In Japan it is known as *kofuki-saru-no-koshikake* and and in China as *shu-she-ling-zhi* (Asian Anticancer Material Database, 2021). No ancient time period had been mention for the traditional medicinal uses of *G. applanatum*.

Lingzhi has been recognized as a medicinal mushroom for over 2000 years, and its powerful effects have been documented in ancient scripts (Wasser *et al.,*2005). In the supplement to *Classic of Materia Medica* (502-536 AD) and the *Ben Cao Gang Mu* by Li Shin-Zhen, which considered to be the first pharmacopoeia in China (1590 AD; Ming dynasty), the mushroom was attributed with therapeutic properties, such as tonifying effects, enhancing vital energy, strengthening cardiac function, increasing memory, and antiaging effects (Wachtel-Galor *et al.,*2011).

Classification (Anand and Chowdhry, 2013; CABI, 2020)

Domain: Eukaryota

Kingdom: Fungi

Phylum: Basidiomycota

Subphylum: Agaricomycotina

Class: Agaricomycetes

Subclass: Agaricomycetidae

Order: Polyporales

Family: Ganodermataceae

Genus: *Ganoderma*

Species: *Ganoderma applanatum*

Binomial name: *Ganoderma applanatum* (Pers.) Pat.

Distribution and Morphology

The mushroom has been reported from different countries of Asia, Europe, North America and South America. Thus their distribution can be considered cosmopolitan (CABI, 2020). In

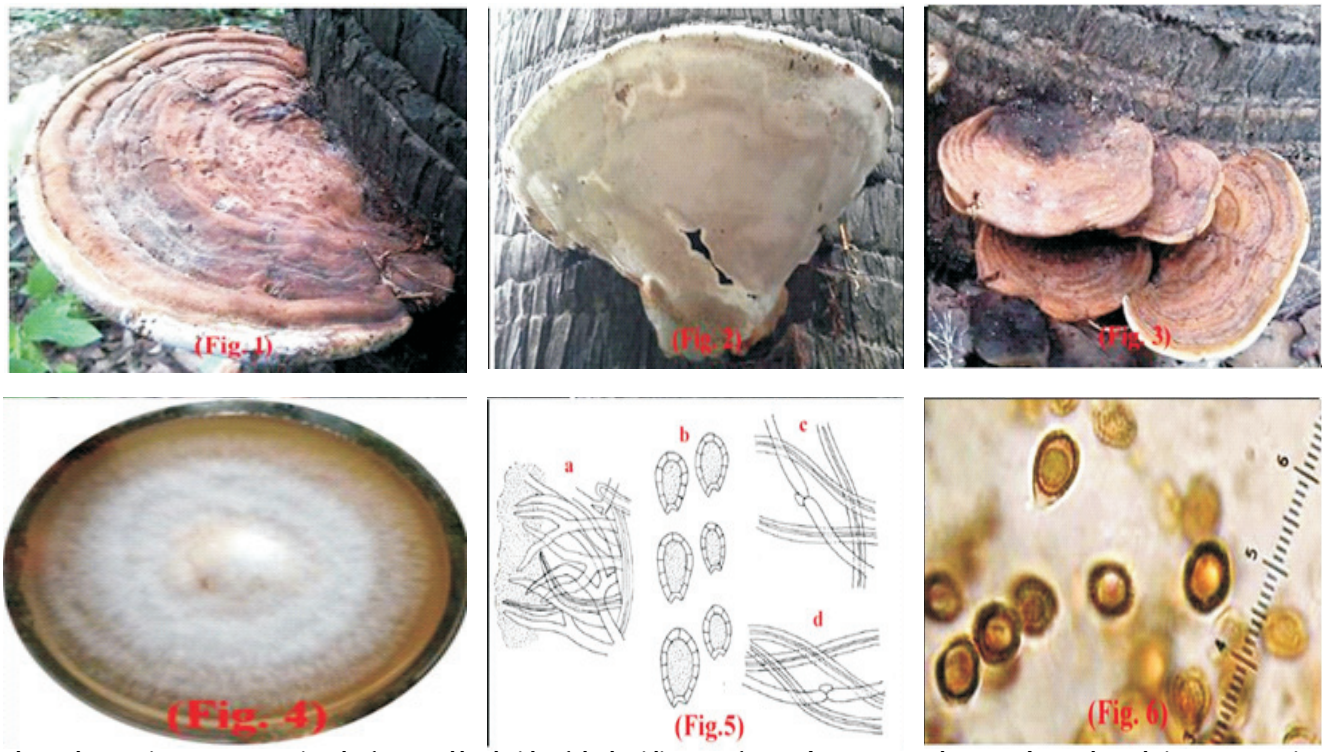

Photo plate 1: Fig.1, 2 representing the front and back side of the basidiocarp of*G. applanatum* (Dandapat *et al.,*2019b) and Fig.3 representing basidiocarp of *G. applanatum* in groups; Fig. 4 diagrammatic representation of the cultured mycelia of *G. applanatum*; Fig. 5 showinghyphae of the cutis (a), basidiospores (b), tube layer hyphae (c) and context hyphae (d) of*G. applanatum* (Saha *et al.,*2018); Fig. 6 microscopic view of spores of *G. applanatum* (Kuo M, 2018).

India this taxon was previously reported from Maharashtra, Dehradun, Punjab, Assam and Jharkhand (Saha *et al.,*2018; Dandapat *et al.,*2019).The macrofungus is saprobic, perennial but releasing spore in summer and autumn. *G. applanatum* grows alone or in groups on dead logs of hardwood, sapwood and conifers, also on living trees (Anand and Chowdhry, 2013).

The term *Ganoderma* is derived from the Greek word *ganos*: shining and *derma*: skin.The mushroom *G. applanatum* has been identified on the basis of morphology and reported from time to time. The bases of morphological identification are basediocarp, hyphal system and spores. The report on identification of *G. applanatum* by different workers is presented in Table-1 and Photoplate-1includes the list of identified structure of *G. applanatum*.

Table 1: Description of *G. applanatum* basediocarp, hyphae and spores.

Sl. No.	Basediocarp	Hyphal system	Spore	References
1	Dull grey, grey-brown to brown, fan shaped, hard woody in texture. Size: 5.7-6.2cm broad × 5.5-11 cm thick. Pores: 4.2-5.8 per mm, white.Multi-seried tubes: 3.7-14 mm long, separation of a thin tissue layer.	No description	Brown, elliptical, blunt at the distal end, thick-walled, ornamented with minute spines.	Anand and Chowdhry, 2013
2	Sessile, dull, non-laccate, woody, applanate. 50–86 × 30–35 mm in diameter and 35–44 mm thick. Upper surface greyish to reddish-brown with concentric zonation, whitish pore surface.	Trimitichyphal system. Yellowish-brown generative hyphae:thin walled, 4.5–5.5 ¼m wide, clamp connection present at septa.Dark brown branched skeletal hyphae: 4.5–6 ¼m wide, and the hyaline binding hyphae: branched, 1.7–2.5 ¼m wide.	Basidiospore:double walled, truncate 7.5–9× 3.5–4.5¼ mdiameters. , Exospores: hyaline, thin walled.Endospore: pale yellow to dark brown, elongated ridges	Saha *et al., 2018*
3	Semicircular, 10–30 cm across, 8–14 cm deep, dull, unvarnished outer crust surface, furrowed in zones ,brownish to grayish brown. white pore surface, dirty brown in age, with 4–6 tiny circular pores per mm.	The older layers of tube often stuffed with white mycelial material.	Ellipsoid, a truncated end, double-walled, brown to orangish brown, 6–9 x 4–5 μm	Kuo M., 2018
4	15 to 50cm across and 5 to 10cm thick, off-white margin and a brown top.Lower surface with small round pores, typically five per mm, are white when the fruiting body is young, turning brown with age or when bruised.	No description	Brown, Ellipsoidal to ovoid, truncate at one end, smooth,6.5-8.5 x . 4.5-6¼m	Paul*et al.,* 2008; First Nature, 2021.
5	3–30 cm wide × 5–50 cm long × 1–10 cm thick, hard as leather, woody. The tubes are 4–12 mm deep and terminate in pores that are round with 4–6 per millimetre.	No description	Brown spores were released from the pores on the underside of the fruiting body.	Ginns J, 2017; Meuninck J. 2017
6	Semicircular, 13 cm in diameter,wrinkled zones of brownish to greyish-brown colour at outer surface and the lower surface is white.	No description	No description	Dandapat *et al.,* 2019b.

Culture and Growth

Microbial culture media can be of different type, depending on the nutritional growth requirements of the microorganisms. Microorganisms require about 10 macro elements namely C, O, H, N, S, P, K, Ca, Mg and Fe. The first six components are used in the synthesis of Carbohydrates, Lipids, Proteins and Nucleic acids and the remaining four exist in the cell as cations and play a variety of roles. In addition to macroelements, microelements like Mn, Zn, Co, Mo, Ni and Cu are also required and they are generally part of enzymes and cofactors. Microorganisms also require growth factors, which are organic compounds (Basu *et al.,*2015)

A culture media used for the *in vitro* culture of fungal mycelia is composed of four basic components- essential elements and minerals, an organic supplement supplying vitamins and amino acids, a source of fixed carbon and a gelling agent (Ajdari *et al.,*2011; Kumar and Mina, 2019). In addition, various types of C and N sources could be utilized by fungi due to their ability in secreting various enzymes for the degradation of the polymers into small molecules (Lee *et al.,* 2007). This means that the type and concentration of C and N sources, C/N ratio, and vitamins are the important factors in medium formulation for the enhancement of fungal growth and sporulation. Although potato dextrose agar (PDA) and malt extract agar (MEA) are generally known as the most common media for growth and sporulation of fungi (Carvalho *et al.,* 2005) they are only suitable for laboratory scale and might not be economic at large-scale production. However microorganisms flourish at different environments and have some environmental growth requirements like pH, osmotic conditions, light and temperature.

Woo-Sik Jo *et al*. (Woo-Sik *et al.,*2009) conducted an experiment to obtain basic information regarding the mycelial culture conditions of *Ganoderma applanatum*. They focused mainly on the effects of pH, temperature, culture media, and effects of nutrient sources such as carbon, nitrogen, carbon/ nitrogen ratio, vitamins, organic acid and mineral salt on the growth of *G. applanatum* mycelia. They reported 6-9 pH, 25-30ºC temperature, PDA, YMA (yeast malt agar), MCM (mushroom minimal media) and dark conditions showed maximum growth of *G. applanatum* mycelia. They also found among the used 10 carbon sources mannose, among the 13 nitrogen sources yeast extract, 5:1 C/N ratio, vitamins like thiamine-HCl and biotin, organic acid like succinic acid and lactic acid, salts like $MgSO_4$, 7H2O, KH_2PO_4 and NaCl were showed excellent growth of *G. applanatum* mycelia.

In a similar work on mycelial growth of *G. applanatum* for exo-polymer production, (Yong *et al.,*2009) it was reported that the growth of *G. applanatum* mycelia was highest and a pH of 4 to 6. Glucose served as a main carbon source among the studied five different carbon sources (glucose, maltose, arabinose, mannose and molasses) and corn steep powder served as main nitrogenous source among other studied nitrogen sources (yeast extract, peptone, meat extract, malt extract) for the maximum production of mycelia (10.65 g/L to 11.87 g/L). It was also reported maximum yield of mycelia (18.0 g/L) was achieved at the end of log phase (12 days).

Mycochemistry of *G. applanatum*

Woody mushrooms normally grow as parasites or saprophytes on living trees or sometimes associated with logs of wood and tree stumps. Species of *Ganoderma* are well known to cause different types of rots by decomposing lignin as well as cellulose and other related polysaccharides in both angiosperm and gymnosperm hosts (Singh *et al.,*2014).Some species of *Ganoderma* have been reported to contain different chemical constituents such as polysaccharides, proteins, amino acids, fatty acids, terpenoids, steroids, alkaloids, phenolic compounds, *etc*. (Paterson, 2006; Boh *et al.,* 2007) with anti-inflammatory, anti-tumor, anti-oxidant, immun omodulatory, anti-diabetic, anti-viral, anti-bacterial, anti-fungal properties (Paterson, 2006; Kao *et al.,* 2013; Singh *et al.,*2014).

Production of secondary metabolites is a common feature of fungi. It consists of a relatively small number of enzymological processes which convert a few important intermediates of primary metabolism into a wide range of products (Bu'Lock, 1961).Furthermore, fungal secondary metabolites are derived from a few common biosynthetic pathways which branch off the primary metabolic pathways and are often produced as families of related compounds, often specific for a group of organisms (Dewick P.M., 2009). The MVA and MEP pathway, the shikimic acid pathway, the acetate pathway are the major pathways for the synthesis of fungal secondary metabolites such as terpenoids, aromatic amino acids and phenylpropanoids, polyketides respectively. Fungal alkaloids are commonly produced from amino acid through terpenes or acetate pathway (Hansoon D., 2013).Qualitative biochemical screening of different solvent extracts of *G. applanatum* fruiting body were carried out and found the extracts of this mushroom carry wide range of primary as well secondary metabolites such as carbohydrates, proteins, amino acids, lipids, steroid, terpenoids, alkaloids, phenolic compounds, tannins, flavonoids, saponins, glycoside etc (Singh *et al.,*2014; Nagaraj *et al.,*2013;Dandapat*et al.,* 2019b).

Two new benzopyran-4-one derivativesapplanatin A ($C_{16}H_{16}O_6$), B ($C_{16}H_{18}O_6$) and a ganoderma aldehyde commonly known as ganoderenic acids were isolated and identified by column chromatography and ^{13}C NMR from chloroform-methanol extract of fruiting bodies of the fungus *G.applanatum* (Wang *et al.,* 2007).Palmitic acid is a major antibacterial compound that was isolated, quantified by HPLC and TLC from methanolic extract of *G. applanatum* and the molecular structure of the compound was determined by Mass and ^1H NMR spectroscopy (Moradali, 2008).By using GC-Mass and H_1NMR bioactive chemical compounds G1 ($C_{20}H_{34}O_4$) with chemical structure [(19,19a-dihydroxy-2-methyl-2,3,4, 5,6,7,8,9,10,11,12,13,14,15 tetrad ecahydrobenzo[b] oxacycloheptadecin-17(19aH] belongs to tannin group and another compound G2 ($C_{21}H_{28}O_2$) with molecular structure[(2-(2-(2,5- dihydroxyphenyl) ethylidene)- 11-hydroxy-6,10-dimethylundeca-5,9-dienoic acid] belongs to terpenoides group were isolated and identified from the mycelia culture of *G. applanatum* which showed potent bactericidal activity (Muhsin *et al.,* 2011).

A chemical analysis of ethanolic extract of mushroom *G. applanatum* was carried out through gas chromotaghrophy coupled to mass spectrometry and first time reported six new compounds:4-metil-ergosta-22-en-3 α -ol; 4,4-dimetil-ergosta-5,7,25(26)-trien-3 -ol; ergosta-5,7,9,24(28)-tetraen-3 α –ol; 4,4-dimetil-ergosta-7,24(28)-dien-3 –ol; 17-isopropil-″5,7-3-odroxiandrostadieno;and estigmasta-5,22-dien-3 a–ol (Guzman *et al.,* 2013). In another study GCMS analysis of methanolic extract of *G. applanatum* was performed and identified some principal components a-terpinene, D-limonene, cis-2-methyl-4-pentylthiane-s, s-dioxide, α -cymene and -terpinolene which possessed cytotoxic potential on different tumour cells (Hakkim *et al.,* 2016).

Quantitative estimation of secondary metabolites of mushroom *G. applanatum* has been done from different regions of world and the results showed variation in the amount and composition of secondary metabolites.Nagaraj *et al.*(2014), estimated phenol (71 ± 0.02 μg/mg) and flavonoid (45 ± 0.01μg/mg) in high quantity compared to tannin (12.82 ± 0.02μg/mg), saponin (5.91 ± 0.01μg/mg) and steroid (13.45 ± 0.01μg/mg) from methanolic extract of *G.applanatum*. In a similar study Rajoriya *et al.* (2015) quantified proximate secondary metabolite from *G. applanatum* fruiting body. They found phenol (11.60 ± 0.20 mg/g), caretonoid(7.43 ± 0.29 mg/g) and alkaloid (4.40 ± 0.25 mg/g) in high amount compared to the other trace metabolites such as -carotene, lycopene, ergosterol, tannin, ascorbic acid and flavonoids. Mohammadifar *et al. (*2020) also performed a comparison study between antioxidant activity and bioactive compounds of *G. applanatum* and *G. lucidum* and reported the extract of *G. applanatum* contain 6.70 mg/g phenolic compound and 1.37 mg/g flavonoid compound. They also quantified terpenoid acids,ursolic acid and oleanolic acid in trace and 1.55mg/g betulinic acid by HPLC method.

Pharmacological and medicinal activities

Antimicrobial activity

G. applanatum possess a wide range of bioactive compounds and they showed broad spectrum antibacterial, antifungal and antiviral activities. The mushrooms showed antibacterial activities against both gram-positive and gram-negative bacteria (Gao *et al.,*2005). Artur *et al.,*(1999), studied the bactericidal activity of isolated sterols 5 α -ergost-7en-3 α -ol, 5 α -ergost-7,22-dien-3 -ol, and 5,8-epidioxy-5 α ,8 α -ergost-6,22-dien-3 -ol against pathogenic ATCC and MIP strain bacteria Bacillus cereus, Corynebacterium diphtheria, E. coli, *P. aeruginosa* , *Staphylococcus aureus* , *Staphylococcus saprophyticus* , and *Streptococcus pyogenes*. They reported gram-positives bacteria were more sensitive (MICs of 0.003 to 2.0 mg/mL; MBCs of 0.06 to 4.0 mg/mL) than the gram-negative bacteria (MICs of 1.0 to 4.0 mg/mL; MBCs of 2.0 to > 4.0 mg/mL).

The crude extracts of *G. applanatum* are also well known for their antimicrobial activities. A broad range of antibacterial and antifungal activity of petroleum ether, chloroform, methanolic and aqueous extracts of *G. applanatum* fruiting body were screened against MTCC pathogenic bacteria *S. aureus, B. subtilis, E. coli, P. aeruginosa, K. pneumonia, S. typhi* and four dermatophytic fungi *C. albicans,C. indicum, T. rubrum* and *M. gypseum* by agar well diffusion method (Nagaraj *et al.,* 2013). Among the studied bacteria *S. typhi* showed lowest inhibitory effect against all the extracts (only 8 ±0.24 mm zone of inhibition against methanolic ectract) and *S. aureus* showed highest sensitivity (15±0.21 mm to 8± 0.21 mm zone of inhibition) against all the studied extracts. Among the studied fungal strains *C.albicans* (10± 0.23mm to 5± 0.2mm ZOI) and *C.indicum* (7± 0.18 mm to 5± 0.1 mm ZOI) showed high inhibition to all the extracts.

Monika *et al. (*2014), studied the antibacterial activity of isolated exopolysaccharide from stationary cultures of *G. applanatum* against *E. coli* and *S. aureus* strains. The exopolysaccharide showed 17.9mm inhibition zone of and 1mg/mL MIC against *S. aureus* but no inhibition was observed against *E. coli*.

Bactericidal activities of purified polysaccharides and hot alkali extract of wild *G.applanatum* were examined against some other bacterial species such as *Listeria monocytogenes, Geobacillus stearothermophilus, Enterococcus faecalis*, *Proteus hauseri*, *Salmonella enteritidis*, *Shigella sonnei* and *Yersinia enterocolitica*(Klaus *et al.,*2016) and found the alkali extract (MIC: 0.039 mg/mL to 1.25 mg/mL; MBC: 1.25 mg/mL to 10.0 mg/mL) was most effective than the partially purified polysaccharide (MIC: 0.156 mg/mL to 5.0 mg/mL; MBC: 2.5 mg/mL to 10.0mg/mL). Bacterial growth inhibitory activity of methanol, ethanol, chloroform and aqueous extracts *G.applanatum* has been studied by agar well diffusion and broth dilution method against urethitis, cystitis, prostatitis and pneumonia causing bacteria *Proteus mirabilis* (Dandapat *et al.,* 2016) and has been found that all the extracts, in both the methods adopted, showed 100% inhibition indicating 1.98± 0.01 to 3.02 ±0.03 mm ZOI with 800 μg/mL MIC.

It is reported that antimicrobial compounds such as terpenes, lectins, polysaccharides etc. act on the bacterial cytoplasmic membrane to make them more permeable for autolysis (Lin and Chou, 1984; Yang *et al.,* 2002; Qureshi *et al.,* 2010). It has been experimentally reported the *Ganoderma* mycelia and fruiting body extracts inducing protein leakage within bacterial cells due to their rich content of flavonoids and nucleobases (Mishra *et al.,* 2018). During pathogenic invasion extract of medicinal mushrooms induced generation of free radicals such as reactive oxygen species, peroxide radicals, and superoxide radicals etc. within bacterial cells, leading to cellular membrane damage as well damage intra cellular components such as DNA, intermediate enzymes involve in membrane synthesis *etc* (Zhang *et al.,*2015; Mishra *et al.,*2018).

Viral infections are amongst the most common diseases affecting people worldwide. New viruses emerge all the time and presently we have limited number of vaccines and only few antivirals to combat viral diseases. Fungi represents a vast source of bioactive molecules, which could potentially be used as antivirals in the future (Rikka *et al.,* 2018).Antiviral activity of *G. applanatum* has not been widely explored. Elkhateeb *et al.,* (2020) studied the antiviral activity of methanolic extract *G. applanatum on* simian rotavirus SA-11 strains by MTT assay method and they found the extract exhibited TI (CC_{50}/IC_{50}) = 3.4 against virus infection.

Antioxidant activity

Antioxidants are any substance, that delays, prevents, or removes oxidative damage to a target molecule (Halliwell B., 2007).Antioxidant compounds are broadly classified into natural or primary and synthetic or secondary antioxidants. They are the chain breaking molecules which react with free radicals and convert them into more stable products. They are mainly derived from the natural sources such as antioxidant minerals, vitamins, secondary metabolites of plants and higher fungi *etc*. Secondary antioxidants are compounds that perform the function of capturing free radicals and stopping the chain reactions and include compound such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), tertiary butyl hydroquinone (TBHQ), nordi hydroguaiaretic acid (NDGA) *etc* (Carocho *et al.,*2013; Rasheed *et al.,* 2019).

Oxidative stress is a phenomenon caused by an imbalance between production and accumulation of free radical species (reactive oxygen species, reactive nitrogen species, reactive sulfur species, reactive carbonyl species *etc*.) in cells and tissues and their intensity wise ranging from physiological oxidative eustress to excessive and toxic oxidative distress (Yan L.J., 2017). Free radicals are generated from both endogenous and exogenous sources. Immune cell activation, inflammation, ischemia, infection, cancer, excessive exercise, mental stress, and aging are all responsible for endogenous free radical production. Exogenous free radical production can occur as a result from exposure to environmental pollutants, heavy metals, certain drugs, chemical solvents, cigarette smoke, alcohol, and radiations *etc.* (Valko*et al.,* 2006; Valko *et al.,* 2007).

At low or moderate concentrations, free radicals play several beneficial roles such as elimination of intracellular pathogens, tumor cells, and play regulatory role in intracellular signaling cascades (Pizzino *et al.,*2017). Oxidative distress is associated

with several patho-physiological conditions and one on the leading cause of cardiovascular diseases, chronic obstructive pulmonary disease, chronic kidney disease, neuro degenerative diseases, and cancer including sarcopenia and frailty *etc*. (Liguori *et al.*,2018).Chemical composition and antioxidant potential of mushrooms have been intensively studied and found edible mushrooms might be used directly in enhancement of antioxidant defenses through dietary supplementation to reduce the level of oxidative stress. Wild or cultivatedmushrroms have been related to significant antioxidant properties due to their bioactive compounds, such as polyphenols, polysaccharides, vitamins, carotenoids and minerals (Kozarski *et al.*,2015).

In vitro antioxidant activity of *G. applanatum* petroleum ether, chloroform, methanol and aqueous extract were determined by DPPH scavenging assay, reducing power assay, metal chelating assay, hydroxyl radical scavenging assay, superoxide radical scavenging assay. The methanolic extract showed higher DPPH radical scavenging activity (IC_{50}:135.13 μg/mL), ferric reducing activity (0.85%), Fe^{2+} chelating activity (IC_{50}: 50.84 μg/mL), compared to the other extract, hydroxyl radical scavenging activity (IC_{50}: 104.89 μg/mL to 112.78 μg/mL), superoxide radical scavenging activity (IC_{50}: 111.94 μg/mL and 120 μg/mL) compared to the other extract (Nagaraj *et al.,* 2014).Rajoriya *et al.*(2015),studied and reported *G. applanatum* methanolic extract showed 91.64% DPPH radical scavenging activity with IC_{50} = 6mg/mL.Antioxidant activity of exoploysaccharide of *G. applanatum* mycelia was studied and reported, the exopolysaccharides of *G. applanatum* strain effectively scavenged hydroxyl radicals (63.9 $\pm$ 0.1%) and superoxide anion radicals (58.8 $\pm$ 0.1) (Liu *et al.,* 2015).

Anticancer activity

Cancer is a major public health problem, being one of thehighest causes of death in both men and women in developed as well as developing countries (Baliga *et al.,* 2012; Rahman *et al.,* 2014). Approximately 12.7 million new cancer cases and 7.6 millioncancer deaths occurred near 2008. By the year 2020, predictions report that the incidence of cancer may increase 3-fold, with a disproportionate rise in cancer cases and deaths in developing countries (Rahman *et al.,* 2014).Cancer occurs by successive mutations in genes that changes cell functions. Chemical compounds have an obvious role of forming gene mutations and cancer cells but other factors such as smoking,viruses, bacteria, and radiation rays are other carcinogenic factors, comprising about 7% of all cancers (Parkin D.M., 2006; Rahman *et al.,* 2014). In general, cancer disrupts cellular relations and results in the dysfunction of vital genes and this disturbance is affective in the cell cycle, and leads to abnormal cell proliferation (Seto *et al.,* 2010; Rahman *et al.,* 2014).

Cancer in the broader sense refers to more than 277 different types of cancer disease. In men commonly the highest percentage of cancer occurs in the prostate, lung and bronchus, colon and rectum, and urinary bladder, and in women most prevalence cancer occur in the breast, lung and bronchus, colon and rectum, uterine corpus and thyroid (Siegel *et al.,* 2016;Rahman *et al.,* 2014) . For children, the highest percentage types of cancer are blood cancer, and cancers related to the brain and lymph nodes (Rahman *et al.,* 2014). Chemical drugs for cancer treatment, such as cisplatin and cyclophosphamide, can cause side effects, such as nephrotoxicity, which are detrimental to the quality of life of patients (Aguirre *et al.,* 2013). In addition to this toxicity, the resistance of some cancer cells to treatment has led to the need for the evaluation of alternative approaches (Yu *et al.,* 2018).

It has been reported the anti-cancer compounds of mushroom play crucial role as reactive oxygen species inducer, mitotic kinase inhibitor, anti-mitotic, angiogenesis inhibitor, topoisomerase inhibitor, leading to apoptosis, and eventually checking cancer proliferation (Patel *et al.,* 2012).The main *Ganoderma* species are *G. lucidum, G. sinensis, G. applanatum, G. tsugae, G. atrum, G. formosanum, G. microsporum,* and *G. atrum*. They have been studied and broadly explored for anticancerous and other medicinal properties (Yu *et al.,* 2018).

Antitumor effect of exo-polymer produced by *G. applanatum* was investigated using sarcoma-180 bearing mice and significant growth inhibition of solid tumor and increase natural killer (NK) cell activity as well phosphatase activity was found (Yong-Tae *et al.,* 2008). Antitumor activity of extracellular polysaccharide from cultured mycelia of *G. applanatum* was investigated *in vitro* by MTT assay against cervical carcinoma cell lines SiHa and CaSki (Monika *et al.,*2014). A significant cytotoxic activity with 42.8% and 34% decrease in cell viability of SiHa carcinoma at 22.88 5μg/mL and 228.5 5μg/mL concentrations of the exopolysaccharides was observed respectively. It has been reported that polysaccharides from *Ganoderma* species inhibited tumor growth via induction of apoptosis through mitochondrial pathways and immuno enhancement effects (Li *et al.,* 2011).A dose dependent anti-proliferative activity of terpenoid compounds from methanolic extract of *G. applanatum* was studied against triple negative breast cancer cells (MDA-MB-231) and cervical cancer cells (HEp-2) and found after 24 hours of treatment the carcinoma cells lost their adherence and morphology and were found to be necrotic (Faruck *et al.,* 2016). Recently both *in vivo* and *in vitro* anticancer study of *G. applanatum* secondary metabolites was carried out and reported that the *G. applanatum* inhibit the proliferation and viability of colon cancer cell (Ccco-2) and decrease the volume of solid developed Ehrlich tumor by activating apoptosis through p53-independent and p53-dependent path ways (Elkhateeb *et al.,* 2018).

Anti-inflammatory activity

Inflammation is considered to be part of the complex biological response to remove injury or harmful stimuli such as pathogens, damaged cells, or irritation. Inflammation leads to many physiological symptoms such as fever, pain, and swelling, vasodilation, increased vascular permeability *etc*. In recent era nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat inflammation but long-term use of NSAIDs induce side effects such as mucosal lesions, bleeding, peptic ulcers, intestinal perforation *etc*. (Sinha *et al.,* 2013). Side effects of NSAIDs are not limited only to GI-tract but extend to serious situations such as acute renal failure, nephrotic syndrome, hypertension, and cardiovascular toxicity *etc*. (Meek *et al.,* 2010).

Anti-inflammatory effects with anti-inflammatory compounds of mushrooms involve a highly diversified group of biochemicals. They include polysaccharides, terpenoids, phenolic compounds, and many other low molecular weight molecules (Elsayed *et al.,* 2014).*Ganoderma extract* treatment leds to significant increases in the percentages of CD^{4+}, CD^{25+}, $Foxp^{3+}$, Treg and IL-10^{+} Breg cells, together with a reduction in the plasma concentrations of several inflammatory cytokines and down-regulated expression of the corresponding cytokine related genes in systemic lupus erythematosus include inflammation of the joints, joint pain, and edema (Cai *et al.,* 2016).In an *in vitro* experiment ethanol extract of *G. applanatum* showed dose dependent anti-inflammatory activity. The ethanol extract of *G. applanatum* at a dose of 600 mg/kg showed maximum suppression of oedema (59.2%) in the rat paw. Along with anti-inflammatory activity the extract also prolonged the reaction time in mice to noxious thermal stimuli (Ede *et al.,* 2012).

Antidiabetic activity

Diabetes mellitus is a group of physiological dysfunctions characterized by hyperglycemia resulting directly from insulin resistance, inadequate insulin secretion, or excessive glucagon secretion. Type-1 diabetes (T1D) is an autoimmune disorder leading to the destruction of pancreatic beta-cells and type-2 diabetes (T2D) is most common and is primarily a problem of progressively impaired glucose regulation due to a combination of dysfunctional pancreatic beta cells and insulin resistance (Blair M., 2016). Due to imbalance of specific receptors such as Glucagon-like peptide-1(GLP-1) receptor, peroxisomes proliferator activated (a) receptor (PPARa), beta3 (α 3) ardent-receptor some enzymes like α glycosidase, dipeptidyl peptidase IV enzyme *etc*. can cause diabetes mellitus (Nishita *et al.,* 2016).

In vivo antidiabetic activity of *G. applanatum* extract and secondary metabolites has been studied on streptozotocin and alloxan induced diabetic animal. Streptozotocin is a glucosamine nitrosourea compound that induces diabetes either by inactivation of the GLUT2 glucose transporter receptor of α -cells or by the destruction of α - cells (Graham *et al.,* 2011). Alloxan is a pyrimidine, structurally similar to glucose and uric acid directly disrupt α -cell membrane permeability and inhibition of tricarboxylic acid cycle and Ca^{2+}- dependent dehydrogenases in the mitochondria causes ATP deficiency, cessation of insulin production, and eventual α -cell death (Schmeltz *et al.,* 2006). Hossain *et al*., (2021) reported very effective impact on blood glucose levels in experimental rats as presented in Table 2.

Ganoderma applanatum exo-polymer (GAE) produced by submerged mycelial cultures substantially reduced the plasma glucose levels by as much as 22.0% in streptozotocin induced diabetic rats, when compared with the control group (Yang *et al.,* 2007). Oral glucose tolerance test is a standard procedure to identify persons at high risk for type-II diabetes (Stern *et al.,* 2002). It is a widely utilized method which has been used to evaluate the α -cell function and insulin resistance (Stumvoll *et al.,* 2000). *G. applanatum* methanolic and chloroform extracts(500mg/kg b.wt.) also significantly maintained the glucose homeostasis in alloxan induced diabetic rats by inhibiting the rise in plasma glucose levelscompared to post versus pre-prandial plasma glucose levels which is nearly similar to normal control and positive control rats. The presence of various secondary metabolites helps to restore the capacity of pancreatic α -cells, stimulating insulin secretion and glucose uptake by the peripheral tissues (Ruby *et al.,* 2018; Hossain *et al.,* 2021).

Hepatoprotective and Nephroprotective activity

The liver is one of the most important organs of the body and performs elementary role in the regulation of different physiological processes, and its activity is related to different vital functions, such as metabolism, secretion, and storage.Hepatic diseases continue to be among the principal threats to public health, and they are a problem worldwide (Adewusi and Afolayan, 2010; Madrigal-Santillan *et al.,* 2014). Hepatic disease is a term that indicates damage to the cells, tissues, structure, or liver function, which can be induced by biological factors (bacteria, virus, and parasites) and autoimmune diseases (immune hepatitis, primary biliary cirrhosis), as well as by the action of different chemicals, such as some drugs (high doses of paracetamol and antitubercular drugs), toxic compounds (CCl4, thioacetamide, dim ethylnitrosamine, D-galactosamine/lipopolysaccharide), and unquestionably, excessive consumption of alcohol (Deshwal *et al.,* 2011; Madrigal-Santillan *et al.,* 2014). Injury to the liver, whether acute or chronic, eventually results in an increase in serum concentrations of total bilirubin (TB), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) (Gowda *et al.,* 2009). In normal rats *G. applanatum* aqueous extract showed no significant effect on TB, AST, ALT and ALP but significant elevation in serum albumin and protein level was observed (Dandapat *et al.,* 2019). In an experiment significantly decrease AST, ALT, ALP, total bilirubin and increase in albumin level in alloxan induced diabetic rats group was observed compared to the

Table 2: Effect of Methanol extract (MEGA) and Aqueous extract (AEGA)on blood glucose level in different groups of experimental rats (Hossain *et al.*, 2021)

Groups	Blood glucose level (mg/dl)			
	Day 1	Day 4	Day 7	Day 9
I: Normal control	96.50 ± 3.73	99.83 ± 4.96	97.00 ± 3.16	100.17 ± 3.49
II: Diabetic control	285.83 ± 11.48[a]	290.50 ± 9.59[a]	303.50 ± 6.06[a]	305.83 ± 6.05[a]
III: Diabetic + MEGA (250 mg/kg)	135.83 ± 6.79[a]	127.83 ± 5.49[a]	119.17 ± 4.26[a]	108.33 ± 4.32[a]
IV: Diabetic + MEGAb (500 mg/kg)	129.17 ± 2.99[a]	117.50 ± 10.03[a]	108.00 ± 3.03[a]	102.00 ± 3.69[a]
V: Diabetic + AEGA (250 mg/kg)	149.33 ± 4.18[a]	133.00 ± 5.69[a]	127.67 ± 5.96[a]	124.33 ± 4.89[a]
VI: Diabetic + AEGA (500 mg/kg)	142.17 ± 4.17[a]	127.67 ± 4.76[a]	124.33 ± 4.41[a]	110.33 ± 5.82[a]
VII: Diabetic + glibenclamide (1 mg/kg)	123.50 ± 3.73[a]	98.83 ± 7.63[a]	91.33 ± 4.27[a]	86.50 ± 6.22[a]

Groups III, IV, V, VI, and VII compared with diabetic control.[a] = $p < .001$, [b] = $p < .01$, [c] = $p < .05$.

diabetic control group (TB- 1.38 ± 0.18 mg/dL,ALB- 2.87 ± 0.19 mg/dL, AST- 52.33 ± 4.72 mg/dL, ALT- 126.33 ± 5.79 mg/dL, ALP- 248.83 ± 5.46 mg/dL) when treated with 500mg/kg *G. applanatum* methanolic extract (TB-1.35 ± 0.11 mg/dL, ALB-3.20 ± 0.28 mg/dL, AST-25.00 ± 3.74 mg/dL, ALT-98.00 ± 4.38 mg/dL, ALP-224.17 ± 3.87 mg/dL) and aqueous extract (TB-1.33 ± 0.13 mg/dL,ALB-3.20 ± 0.30 mg/dL, AST-30.00 ± 5.10 mg/dL, ALT-98.83 ± 3.25 mg/dL, ALP-228.00 ± 5.22 mg/dL) (Hossain *et al.,* 2021).It has also been reported sulfated *Ganoderma applanatum* residue polysaccharides act as potent antifibrotic agent and reduce histopathological damages, down-regulated cytochrome P450 2E1 expression, reduced serum AST and ALT, improved the anti-oxidative and anti-inflammatory properties, inhibited TLR4/NF-κB signaling pathway, and reduced the release of inflammatory cytokines (Xinling *et al.,*2021).

Chronic kidney disease recognized as a major risk factor for the development of new acute kidney injury, and acute kidney injury now accepted to lead to *de novo* or accelerated chronic and end stage kidney diseases (Ferenbachand Bonventre, 2016).Chronic kidney disease is most commonly attributed to diabetes and hypertension (Coca *et al.,* 2012). Acute kidney injury (AKI) describes a sudden loss of kidney function that is determined on the basis of increased serum urea, creatinine, uric acid levels and oliguria (Gowda *et al.,* 2010;Kellum *et al.,* 2021).Dandapat *et al.,* (2019), reported the aqueous extract of *G. applanatum* showed a nephro protective activity in nomal rat and significantly decrease serum urea (57.62±0.74mg/dL),creatinine (0.86±0.008mg/dL) and uric acid (14.24±0.73mg/dL) level compared to control treatment groups of rat (SU: 62.32±1.17 mg/dL; CRE: 0.93±0.01 mg/dL; UA: 22.5±0.70mg/dL).

Antihyperlipidemic activity

Hyperlipidemia is a medical condition characterized by an increase in one or more of the plasma lipids, including triglycerides, cholesterol, cholesterol esters, phospholipids and or plasma lipoproteins including very low-density lipoprotein and low-density lipoprotein along with reduced high-density lipoprotein levels (Shattat G.F., 2014). Elevated levels of cholesterol (hypercholesterolemia) and abnormal lipid profiles (dyslipidemia) are important risk factors for cardiovascular disease (CVD) and the most common forms of the CVD are hypertension, coronary heart disease (CHD), stroke, and heart failure *etc* (Mensah and Brown, 2007; Schaiff *et al.,* 2008).*In vitro* hypocholesterolemic activity of *G. applanatum* extract was studied and reported that the cholesterol reduction activity increases proportionally with the increase in concentration of the extract, and elongation of incubation time (90.9±1.0% to 100.0±0 % reduction after 96 hours) (Elkhateeb *et al.,* 2020).Hossain *et al.,* (2021),reported methanolic extract of *G. applanatum* significantly decrease total cholesterol, LDL cholesterol and triglyceride in extract treated diabetic rats (TC: 48.83 ± 2.79 mg/dL, LDL-C: 11.83 ± 2.32 mg/dL, Triglyceride: 81.50 ± 2.74)compared to control rats (TC: 66.83 ± 2.71mg/dL, LDL-C: 26.67 ± 3.01mg/dL, Triglyceride: 107.50 ± 4.14mg/dL). However a significant increase in HDL cholesterol (31.50 ± 1.87 mg/dL) of extract treated diabetic rats was observed compared to control group (28.00 ± 1.41 mg/dL).

The suppression of LDL oxidation by *G. applanatum* may reduce the serum LDL significantly. Low triglyceride levels can contribute to decreasing the availability of fatty acids for esterification (Packard *et al.,* 2020), increased catabolism of LDL, activation of tissue lipases, and decreased production of precursors of triglycerides (McCarty, 2001; Packard *et al.,* 2020; Hossain *et al.,* 2021).This observed restoration of the alloxan-evoked changes in the serum lipid profile shows the protective nature and hypolipidemic effect of *G. applanatum*.The suggestion is that reductions in intestinal cholesterol and bile acid absorption after the feeding of *G. applanatum* methanolic extract and *G. applanatum* aqueous extract may represent main mechanism for hypolipidemic mechanisms of *G. applanatum*(Nagaoka *et al.,* 2005; Hossain *et al.,* 2021).

Hypouricemic activity

In recent years, a large body of evidence has accumulated that suggests that hyperuricemia may play a role in the development and pathogenesis of a number of metabolic, hemodynamic, and systemic pathologic diseases, including metabolic syndrome, hypertension, stroke, and atherosclerosis (Billiet *et al.,* 2014). Hyperuricemia has long been established as the major etiologic factor in gout. It is the most well understood and described type of arthritis. Gout is characterized with reoccurring inflammatory arthritis, which is triggered by the crystallization of serum uric acid (SUA) in the joints and is often caused by hyperuricemia (Choi *et al.,* 2005) *G. applanatum* ethanolic and aqueous remarkably lowered the level of serum uric acid via elevated urin uric acid levels in potassium oxonate and hypoxanthine induced hyperuricemia mice, there by confirming the uricosuria effect (Yong *et al.,* 2018). Ethanolic and aqueous extract did not decrease the XOD activity; hence the hypouricemia effects of *G. applanatum* may be raised by other methods, such as uricosuria or anti npurine absorption pathways. It has been reported renal transporters, including OAT-1, GLUT-9, and URAT-1, are directly associated with the homeostasis of serum uric acid (Anzai *et al.,* 2010; Yong *et al.,*2018). Both ethanolic and aqueous extract of *G. applanatum* increased the mRNA and protein levels of OAT-1, inducing the remarkably enhanced uric acid excretion by advancing the uric acid transportation through OAT-1. The extracts also enhanced the excretion of uric acid by inhibiting the uric acid reabsorption through GLUT-9. Further more, ethanol extract down regulated the level of URAT-1 protein (Yong *et al.,* 2018). Notably, the upregulation of OAT-1 and down regulation of GLUT-9 and URAT-1 correlated to urine uric acid provided the evidence that the synergistic activity of OAT-1, GLUT-9, and URAT-1 by *G. applanatum* contributed to the uricosuria actions.

Anti- Alzheimer's activities

Alzheimer's disease (AD) has progressive neuro degenerative pathology with severe economic and social impact. AD is the dementia associated with aging, which initially targets memory and progressively destroys the functions of the brain, as the neocortex suffers neuronal, synaptic, and dendritic losses. There is currently no cure, although cholinesterase inhibitors provide effective temporary relief of symptoms in some patients (Saify *et al.,* 2014). Treatment of AD has been

dominated by the use of acetylcholinesterase (AChE) inhibitors. These drugs compensate for the death of cholinergic neurons and offer symptomatic relief by inhibiting acetylcholine (ACh) turnover and restoring synaptic levels of this neuro transmitter (Rees and Brimijoin, 2003). Nowadays, drug research and development are based on the cholinergic hypothesis that supports the cognition improvement by regulation of the synthesis and release of acetylcholine in the brain (Saify *et al.,* 2014).Both methanolic and aqueous extract of *G. applanatum* showed cholineesterase inhibition activity but the methanolic extract had high acetyl cholinesterase (1.45 ± 0.01 mg gallic acid equivalents per g extract) and butyryl cholinesterase(2.94 ± 0.19 mg gallic acid equivalents per g extract)inhibitory impact than aqueous extract (Zengin *et al.,* 2015).

Immunemodulatory activity

The human body has a remarkably sophisticated immune system consisting of white blood cells and specialized immune molecules that protect the body against invading pathogens (Yuandani *et al.,* 2021). Several cytokines also play essential roles in immune response, which consist of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-á), interleukin 1 (IL-1), IL-6, IL-11, IL-8, and anti-inflammatory cytokines or cytokines inhibitor such as IL-4, IL-10, and IL-13 (Yuandani *et al.,* 2021). Cytokines as intercellular messenger molecules have several functions, and these include stimulating phagocyte migration and coordinating early responses of monocytes, macrophages, dendritic cells, and lymphocytes during inflammatory states (Shaikh, 2011).Immunomodulators are natural or synthetic substances that modulate or modify the immune response. They help regulate or normalize the immune system by either stimulating or suppressing the immune system (Kumar *et al.,* 2012).

Immunomodulatory activity of *G. applanatum* exopolysaccharide was investigated using THP-1, an acute monocytic leukemia cell line as macrophase model (Monika *et al.,* 2014). They reported, after 24 hours of incubation the extracellular polysaccharides from *G. applanatum* stimulated secretion of IL-6 by macrophages at a level of 328.5pg/mL. The 6-hour incubation of extracellular polysaccharides at a concentration of 228.5 5μg/mL resulted in production of TNF- by 752.17 pg/mL, representing an approximately 54-fold increase compared to the negative but a decrease in the TNF- level to 190.52 pg/mL was observed after 24-hour incubation which was higher in comparison with the negative control.

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