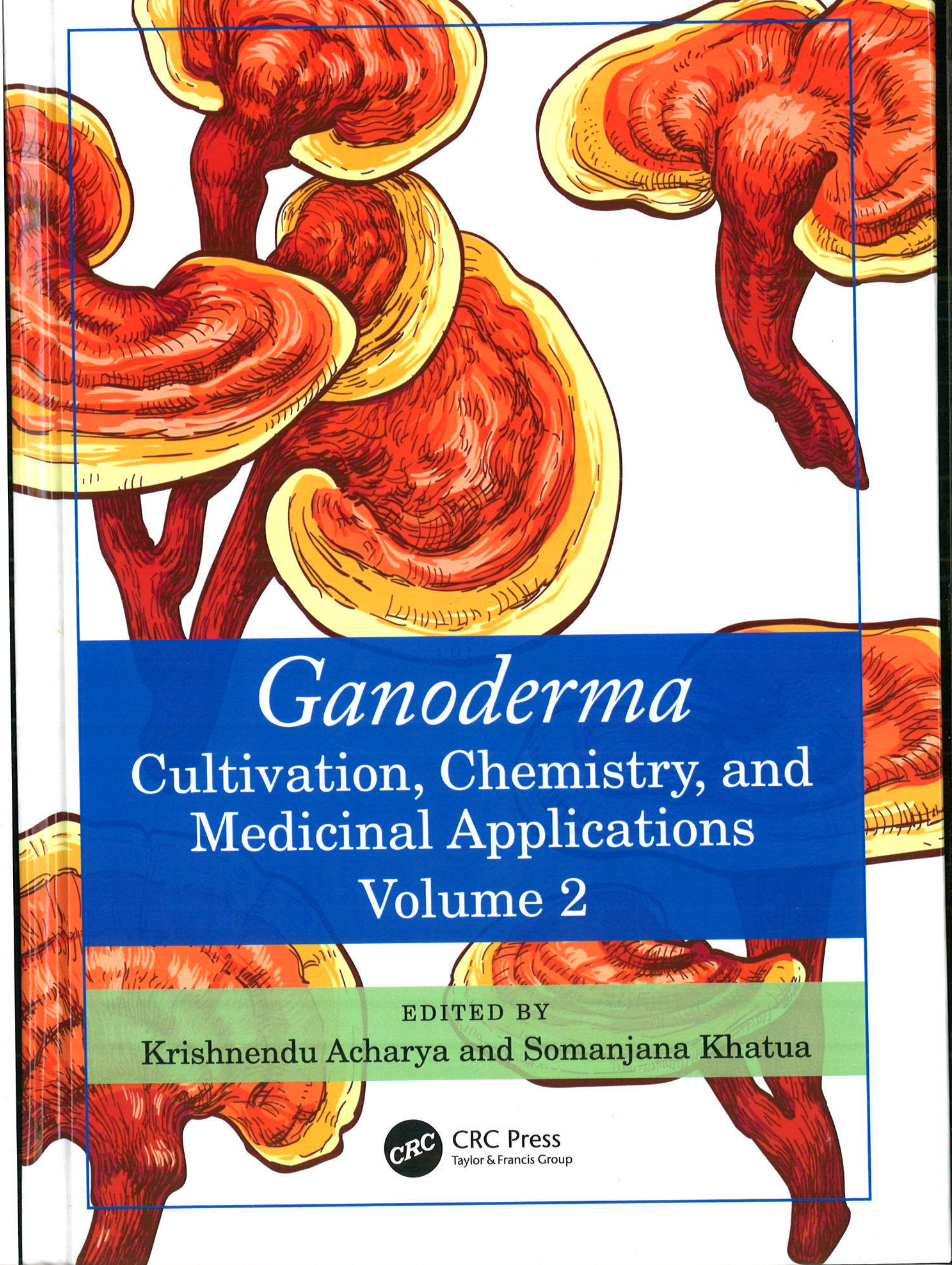

Ganoderma

Cultivation, Chemistry, and Medicinal Applications

Volume 2

EDITED BY

Krishnendu Acharya and Somanjana Khatua

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Ganoderma

For the past two millennia, *Ganoderma* has been prized as the "mushroom of immortality" in ancient Asian cultures, owing to its health benefits. Modern research has further revealed that the genus is rich in bioactive components, including polysaccharides and triterpenoids, uncovering various medicinal prospects both *in vitro* and *in vivo*. Clinical trials conducted so far have emphasized the safe and effective use of the mushrooms, with a particular focus on *Ganoderma lucidum*. Currently, the *Ganoderma*-based industry is witnessing a significant surge, offering a plethora of dietary and medicinal products. Recognizing the impact of these developments, the book *Ganoderma: Cultivation, Chemistry, and Medicinal Applications Volume 2* aims to consolidate the latest information on the macrofungi, emphasizing its bioactive compounds, diverse therapeutic effects, and industrial applications.

Key Features:

- This book provides a thorough exploration of *Ganoderma* polysaccharides, unraveling their chemical composition, structure, and potential health benefits.
- Comprehensive coverage is provided to understand antimicrobial properties of the medicinal mushrooms. The text also delves into the potential role of *Ganoderma* in safeguarding against various skin diseases, accompanied by discussions on underlying mechanisms.
- A detailed examination of *Ganoderma* includes its potential cardioprotective effects, encompassing impacts on blood pressure, cholesterol level, and overall heart function. This book also provides an in-depth analysis of the capacity of the macrofungi to stimulate the immune system.
- The volume encompasses findings related to the impact of *Ganoderma* on prevention or mitigation of neurodegenerative diseases.
- Additionally, it contributes to the understanding of medicinal applications by exploring *Ganoderma*-based nanoparticles, offering novel insights into potential therapeutic avenues.
- A comprehensive overview of the *Ganoderma*-inspired industry highlights its diverse contributions ranging from dietary supplements, cosmeceuticals, and nutricosmetics to healthcare products.

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Preface

Ganoderma, encompassing numerous species, has captivated human curiosity and reverence for millennia. This remarkable macrofungal genus, often referred to as Lingzhi in China and Reishi in Japan, is an emblematic figure in the annals of traditional medicine. Revered as the "mushroom of immortality" and celebrated for its myriad therapeutic virtues, *Ganoderma* has traversed epochs and cultures, leaving an indelible mark on the world of herbal medicine. Such enriched traditional wisdom surrounding the taxon serves as a foundation for contemporary scientific inquiry. Through extensive research, a multitude of medicinal potentials within these mushrooms have so far been unveiled. Amalgamation of the knowledge is highly needed which may form the basis for designing future prospects in herbal medicine. In the pursuit of consolidating this wealth of information, the present book is organized into 11 chapters.

Chapter 1 will take us deep into the molecular intricacies of *Ganoderma* polysaccharides. Their complex, branched, and multifaceted nature has been unveiled delving into the methods used to extract and characterize these enigmatic molecules. The chapter will further explore the diverse therapeutic potential of the bio-polymers suggesting that these macromolecules may hold the key to addressing various health challenges. Chapters 2–4 will offer insights into antimicrobial potential of *Ganoderma* uncovering the diverse arsenal of polysaccharides, secondary metabolites including triterpenes, and other bioactive molecules. From bacteria, viruses, fungi to parasites, antimicrobial activity of members of the genus extends a formidable shield against a wide array of potential threats. The exploration of methods for determination of antibacterial activity has been also a part of the study. The next chapter will transport us into the world of skin diseases and their multifaceted challenges. From common conditions like acne and eczema to more complex disorders such as psoriasis, the potential mechanisms will also be explored by which *Ganoderma* may exert its effects, shedding light on the scientific evidence that informs these hypotheses. The chapter will also delve into the burgeoning market of *Ganoderma*-infused cosmetics and topical formulations. Chapter 6 will take us on a journey through the intricate workings of the heart and the myriad challenges it faces. From hypertension to atherosclerosis and beyond, we will explore the scientific evidence and hypotheses surrounding the potential of *Ganoderma* to safeguard the cardiovascular system. Chapter 7 will shed light on the practical applications of *Ganoderma* in immune health. Several bioactive compounds, β-glucan in particular, have been explored for their ability to induce effects on various innate and adaptive immune cells. The chapter will also discuss about mechanism of action behind such immune-boosting effects. The next chapter will immerse us in the intricate world of the nervous system and its vulnerabilities. From Alzheimer's disease and Parkinson's disorder to other neurodegenerative conditions, the scientific evidence and hypotheses will be explored surrounding the potential of *Ganoderma* to safeguard and support brain health. Chapter 9 will take us into the world of nanoparticles, offering insights into the science of working at the nanoscale. We will explore the techniques employed to extract and manipulate *Ganoderma* nanoparticles, revealing their unique characteristics and bioactivity. Chapter 10 will navigate through the wide array of products that constitute the *Ganoderma*-based industry. From functional foods and beverages to herbal remedies, cosmetics, and more, we will uncover the diversity of offerings that cater to consumers seeking holistic well-being. It will shed light on the economic and market landscape of the *Ganoderma*-based industry. Finally, the last chapter will immerse us in the world of bioactivity of some less-explored *Ganoderma* species, unveiling their potential health benefits and therapeutic properties. It will thus offer insights into the potential applications of these under-utilized mushrooms in various industries.

All in all, the book *Ganoderma: Cultivation, Chemistry, and Medicinal Applications Volume 2* is poised to serve as a valuable roadmap for aspiring young researchers in the realms of functional foods, pharmaceuticals, and nutraceuticals. It also carries the potential to inspire industrialists and scientists to venture into the production of *Ganoderma*-based products, thereby contributing to rural economic development. By offering the latest and most up-to-date information, this book is set to spark fresh ideas for advanced research, bridging the gap between traditional knowledge and evidence-based therapeutics. In this context, we wish to extend our deepest gratitude and respect to all the esteemed contributors who have played a pivotal role in shaping this book. Their timely responses, meaningful contributions, and unwavering support have been instrumental in bringing this project to fruition. It is our fervent hope that this comprehensive resource will prove invaluable to a diverse readership, including students, educators, medical professionals, researchers, and companies engaged in macrofungal research. We anticipate that this book will not only disseminate knowledge but will also inspire future endeavors to harness the potential of *Ganoderma* for the betterment of both human health and rural economies.

Krishnendu Acharya

Somanjana Khatua

Editors

Prof. Krishnendu Acharya pursued Master's degree in Botany from the University of Calcutta. He then completed his M.Tech. and Ph.D. from Jadavpur University. Prof. Acharya joined the University of Calcutta as Lecturer of Botany in 2004 and soon acceded to Professorship in 2012. Till date, he has supervised 22 Ph.D. students and published 475 research articles and 9 books. He has 9,555 Scopus citations and 13,390 Google Scholar citations. His h-indexes are 50 (Scopus) and 59 (Google Scholar), while his Google Scholar i10 index is 259. He was ranked first among top 100 authors of state universities based on Indian Citation Index 2016 by Confederation of Indian Industry (CII). He has been listed on Elsevier's (Stanford University) list of the world's top 2% of scientists for the last 4 years. Prof. Acharya has been elected as a Fellow of the West Bengal Academy of Science and Technology, the Linnean Society of London, the Mycological Society of India, the Indian Mycological Society, and the International College of Nutrition, Canada. He has received many awards, including the Sir Edwin John Butler Memorial Award, the Patel Memorial Award, the Global Achievement in the Field of Phyllosphere Biology, and the Prof. K. Natarajan Memorial Award. He is in the editorial boards of many national and international journals. Prof. Acharya is actively and regularly engaged in lecturing at different seminars, universities, and colleges to boost young minds and inspire students.

Dr. Somanjana Khatua is an Assistant Professor in the Department of Botany, University of Allahabad, Uttar Pradesh, India. She pursued her Master's degree in Botany and Ph.D. from the University of Calcutta. Earlier, she was appointed by West Bengal Education Service and posted in Krishnagar Government College. The areas of her research interest include drug development, immunology, carbohydrate biology, natural products, medical mycology and functional food. Till date, she has published 80 papers in different peer-reviewed journals such as *Current Research in Biotechnology*, *Phytotherapy Research*, *Biodegradation*, *Chemico-Biological Interactions*, *Food and Function*, *Frontiers in Pharmacology*, *Scientific Reports*, *PLoS One*, *Journal of Pharmacy and Pharmacology*, *PeerJ*, *Carbohydrate Polymers*, *Carbohydrate Research*, and *International Journal of Biological Macromolecules*. She has 72 papers in Scopus and 1,448 Scopus citations as well as 1,905 Google Scholar citations. Her h-indexes are 23 (Scopus) and 27 (Google Scholar), while her Google Scholar i10 index is 46. She has received many awards such as Woman Botanist Award 2020 from Indian Botanical Society and Outstanding Paper Award by the Government of West Bengal, India. She has been listed among the top 2% of scientists (rank in a single year 560391) in Elsevier (Stanford University) ranking. She delivers many invited lectures in different colleges across India.

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5 *Ganoderma* in Skin Health Care

A State-of-the-Art Review

Debatri Dewanjee, Sandipta Ghosh, Somanjana Khatua, and Sylvie Rapior

5.1 INTRODUCTION

Skin, the largest organ of human body, functions to protect the body from external environment, aid in regulating fluid and temperature, offer protection from sunlight, and keep out harmful microorganisms (Ribeiro et al., 2015). It is composed of a dense array of extracellular matrix (ECM) proteins, essential for structural and mechanical properties as well as functions of the organ (McCabe et al., 2020). However, maintaining healthy skin is problematic being suffered from both intrinsic ageing (triggered by genetic factors and passage of time) and extrinsic ageing (caused by exposure to smoking, heat, air pollutant, and ultraviolet radiation). As a result, the contents of collagen, elastic fibers, and hyaluronic acid reduce in healthy skin resulting wrinkles, loss of elasticity, dry skin, laxity, and appearance of rough texture (Resende et al., 2021). Moreover, chronic diseases such as diabetes, inflammation, or other diseases can also modify the skin structure (Cooper et al., 2021; Khalid et al., 2022). It is evident that chronic inflammatory conditions disrupt lipid homeostasis of the skin, leading to alterations in lipidome contributing to the development of significant dermatological disorders (Nowowiejska et al., 2023). Such dermal ECM alterations promote age-related skin diseases, for instance, fragility amplification, thinning, impaired vasculature support, and deprived wound healing. Besides the ageing process, metabolic syndromes associated with inflammatory skin diseases are one of the most crucial risk factors for development of skin cancer (Hu et al., 2019; Adibi and Robati, 2021).

To promote the healthy skin, natural products have been used for centuries (Michalak, 2022). The synthetic skincare products contain certain chemicals such as parabens, silicone, and phthalates that may cause a variety of undesirable side effects and potential allergic reactions, particularly for people with sensitive skin. Parabens and phthalates are reported to disrupt hormonal balance and thus indirectly contribute to the development of cancer (Abd Razak et al., 2020). Currently, they are becoming more prevalent in commercial formulations owing to consumers' concerns about synthetic substances and a greater market demand for natural ingredients (Kim et al., 2016). Indeed, it is forecasted that in Europe, sales of natural and organic-based cosmetics are expected to expand 5 billion euros by the end of 2023. In response to the increasing demand, cosmetic brands have begun providing a wider range of natural products and are actively advocating for expanded research into non-toxic, naturally derived ingredients (Abd Razak et al., 2020).

In this context, various substances extracted from macrofungi are now paving their way into cosmetics (Hyde et al., 2010; Bandara et al., 2015; Badalyan et al., 2022). Regarding the Greek etymology of the genus *Ganoderma*, "Ganos" indeed means shiny or bright, while "Derma" refers to skin. Therefore, the name *Ganoderma* can be interpreted as "shiny skin" in reference to distinctive glossy appearance of the mushroom (Wang et al 2020; Galappaththi et al., 2023). A large number of scientific studies have shown that several species of *Ganoderma* such as *G. lucidum*,

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G. resinaceum, and *G. ahmadii* possess strong radical scavenging, antimicrobial, anticancer, and anti-inflammatory properties (Cartigliani et al., 2014; Yang et al., 2019). This review will delve into the prominent constituents found in *Ganoderma* sp., examining their significant effects, including moisturizing properties and their impact on anti-ageing, encompassing aspects like skin-whitening and antioxidant activities. Furthermore, this review will suggest that members of *Ganoderma* and their extracts represent one of the most innovative options for incorporating into cosmetic products.

5.2 COSMETICS, COSMECEUTICALS, NUTRACEUTICALS, AND PHYTOCOSMETICS

As the outer protective surface of our body, the skin is constantly being exposed to daily biotic and abiotic stressors, which can lead to undesirable cosmetic concerns, including development of wrinkles, lesions, rashes, dryness, itching, and a loss of its natural radiance. It is obvious that a healthy and bright skin amplifies beauty irrespective of the real age; to achieve this, skin is the main target to become or even remain more appealing and beautiful. A "cosmetic product" is a substance or mixture intended to be used by means of rubbing, sprinkling, or applying to any part of the human body for the purpose of cleansing, beautifying, promoting attractiveness, modifying appearance of the human body, and keeping skin and hair healthy with mild effect of the substance on any part of the human body (Luque de Castro, 2011). Cosmetics are topical products that enhance appearance and beauty of the human body but do not have any therapeutic effect in contrast to drugs.

Cosmeceuticals are cosmetic preparations with bioactive ingredients claimed to have pharmaceutical properties. They consist of cosmetic products which are applied topically and comprise creams, lotions, and ointments with bioactive compounds influencing biological function of the skin, supplying the needed nutrients for healthy skin, and improving the appearance, radiance, texture, and anti-ageing activity (Taofiq et al., 2017; Espinosa-Leal and Garcia-Lara, 2019; Badalyan et al., 2022; Rashid et al., 2023). The market size of cosmeceuticals is expected to grow from USD 169.48 billion in 2023 to USD 233.30 billion by 2028, at a compound annual growth rate (CAGR) of 6.60% during the forecast period (2023–2028). Additionally, evaluating patterns of absorption and diffusion across membranes, and generating robust prediction models taking into account the intermolecular interactions of bioactive compounds with skin tissue have been described by Aguilar-Toalá et al. (2022).

Nutricosmetics are ingredients or products absorbed orally acting as nutritional supplements to produce a visual effect and improve natural beauty of the skin, nail, and hair (Dini and Laneri, 2019; Perez-Sanchez et al., 2020; Sadgrove and Simmonds, 2021; Anushree and Kambalimatha, 2022; Porębska, 2023). Many micronutrients can provide these benefits: vitamin C has an antioxidant potential and tends to reduce free radical generation when the skin is exposed to ultraviolet (UV) radiation (Pullar et al., 2017). The market size of nutricosmetics is estimated to be USD 8.09 billion in 2023 and is projected to reach USD 11.91 billion by 2028, growing at a CAGR of 8.05% during the forecast period (2023–2028). Following this fashion, the cosmetics industry is also focusing on the development of nutricosmetics and phytocosmetics with high proportions of several constituents from different origins, such as collagen, hyaluronic acid, elastin, and ceramide, known to maintain the structure and function of the skin and hair (Ahmed et al., 2022). Many authors also reported that oral ingestion of nutritious food like prebiotics, probiotics, and fatty acids as dietary interventions may improve water-holding capacity of the skin and its barrier function (Parke et al., 2021; Gao et al., 2023).

5.3 NATURAL VERSUS SYNTHETIC COSMETICS INGREDIENTS

At present, there is an increasing consumer demand for cosmetics comprising natural ingredients as healthier, organic, and ecological products to avoid the damaging effects of synthetic cosmetics (Hoang et al., 2021; Goyal and Jerold, 2023). As such, consumers are more and more refusing synthetic chemicals in beauty and cosmetic products (Amberg and Fogarassy, 2019). The global cosmetic industry is worth tens of billions of US dollars and thus constantly in search of ingredients from natural sources because of their effectiveness, lower toxicity effects, and ability to compete with artificial synthetic counterparts (Taofiq et al., 2017). Application of the natural ingredients like phytonutrients, dairy products, microbial metabolites, minerals and animal protein components, coconut extracts, jasmine, lemon grass, longan and several medicinal plants for skin health care is in current trend because of their ability to protect and treat numerous skin-related diseases and therefore has been extensively investigated in many countries across the globe (De Wet et al., 2013; Rodrigues and Pandya, 2015; Boo, 2020; Pranskuniene et al., 2022).

In this context, herbal medicine, namely, phytotherapy, plays a key role in the daily skin care routine (Bedi, 2002; Binic et al., 2013). For instance, the presence of numerous phenolic compounds in tea, when consumed, is thought to play a significant role in inhibiting enzymes like collagenase, elastase, and tyrosinase. This inhibition helps in preserving the structural stability and elasticity of the skin while also impeding melanogenesis, the process of melanin production responsible for skin pigmentation (Kim et al. 2015; Abd Razak et al., 2019, 2020; Ahmed et al., 2022).

5.4 MUSHROOMS AS FOOD, DRUGS, AND COSMETICS

Mushrooms have grabbed the interest of mankind since time immemorial and have been considered as culinary-medicinal resources in Asian countries like China and Japan to improve their general health, often kept in reserve for the royalty because of their potency and efficacy (Bandara et al., 2015; Thongbai et al., 2015; Hyder and Dutta, 2021). Research has now explored that higher fungi (extracts from fruit bodies, spores, mycelia, or isolated compounds) possess a wide range of therapeutic properties (Diallo et al., 2020; Niego et al., 2021; Badalyan et al., 2023). The development of effective and simple technologies of higher fungi domestication, a range of characteristic features of fungi (fast growth, biomass, and metabolites production), advances in the study of metabolic processes in fungi, introduction of new fungi species to *in vitro* culture, and creation of *in vitro* fungi culture collections have widened the scope of their applications (Bandara et al., 2021; Ofodile et al., 2022; Vasilenko et al., 2022; Kabacia and Muchane, 2023). Mushrooms are hence now finding their ways as a cosmetic ingredient, either as cosmeceutical or as nutricosmetics, and are being used thoroughly as raw material or pure compounds for treating various diseases associated with skin (Wu et al., 2016; Taofiq et al., 2017).

5.5 SKIN AGEING

Skin, the largest organ of the body, accounts for about 15% of the whole weight and functions as the necessary interface between the internal and the external environments (George et al., 2022; Mohamed and Hargest, 2022). Thus, it continuously protects our body from pernicious stimuli, e.g., microorganisms, UV irradiation, allergens, and irritants. It also helps regulate temperature and fluid balance, and prevents water loss from the body (Taofiq et al., 2017; Lawton, 2019). The outermost layer of the skin is called the stratum corneum which is a selectively permeable and heterogeneous layer of the epidermis. The primary function of stratum corneum is to protect the skin against desiccation and environmental challenge as well as to retain sufficient water. Disturbance in skin barrier function is often demonstrated by an altered integrity of the stratum corneum, with a consequent increase in trans-epidermal water loss and decrease in skin hydration (Yoshida et al., 2022). Epidermal stem cells of the skin are responsible for the formation and regeneration of all the different cells in the epidermis. As the skin undergoes continuous differentiation, the epidermal stem cells within the skin bear responsibility for regenerating elastin and collagen fibers. They also contribute to the regeneration of protective barrier of the skin, which in turn helps maintain the overall balance and stability of the epidermal environment, known as epidermal homeostasis. The number of epidermal stem cells decreases with ageing, and accordingly the potentiality of the skin to regenerate get reduced which leads to several barrier disorders like reduction in skin hydration and elasticity forming wrinkled skin. Skin ageing is caused by numerous intrinsic cellular factors as well as many external factors. Intrinsic factors include changes in hormonal secretions occurring with age which results in collagen degradation, dryness, degeneration of elastic fiber networks, and development of wrinkled skin (Papakonstantinou et al., 2012). The extrinsic mechanisms involve overexposure to solar radiation which causes photoageing by oxidative stress. Reactive oxygen species (ROS), originating from oxidative cell metabolism, creates damage to cellular components like cell walls, lipid membranes, mitochondria, and DNA by upregulating elastin and collagen breakdown. Tyrosinase is a key enzyme in melanogenesis pathway, and inhibition of this enzyme is one of the effective therapeutic approaches to control hyperpigmentation such as melasma and age spots (Tief et al., 1996; Pillaiyar et al., 2017). The skin is armed with its natural antioxidant ability which protects itself against these impairments. Since many of the radical scavengers belong to the natural moisturizing factor, also known as NMF family, and mainly contribute to osmotic balance in the skin, the components of skin care products should be adjusted to the NMF, which increases elasticity and smoothness of the skin. Moreover, the inhibitors of enzymes like elastase, hyaluronidase, tyrosinase, and matrix metalloproteinase 1 can be promising cosmetic components in the treatment of skin ageing, thereby reinstating the skin elasticity, increasing moisture content, stimulating collagen synthesis, and producing skin-whitening effect. Hence, there is a huge demand for natural compounds, supplements, or extracts in the cosmetic industry with the ability to delay the ageing process. It has already been reported by several scientists that natural phenolic compounds possess scavenging properties against ROS, which makes them interesting contestants in production of anti-ageing creams or lotions in the cosmetic industry (Soto et al., 2015; Liu, 2022).

5.6 *GANODERMA* EXTRACTS AND INDIVIDUAL COMPOUNDS AS COSMETIC INGREDIENTS

Ganoderma (Lingzhi) from Ganodermaceae family is an edible mushroom belonging to the white-rot fungal group, and has been found to promote health, increase vitality, and prolong life. Indeed, *Ganoderma* has a long history of use in traditional Chinese medicine. More than 2000 years ago, it was documented in the "Shen Nong Ben Cao Jing" (Shennong's herbal classic) and was enlisted as a therapeutic and non-toxic drug. Since 2000, the Chinese pharmacopoeia has recorded fruiting body of *G. lucidum* (Leyss. ex Fr.) Karst (Chi Zhi) and *Ganoderma sinensis* Zhao, Xu et Zhang (Zi Zhi) as the legal traditional Chinese medicine. *Ganoderma lucidum* has been highly regarded as a form of herbal medicine in the historical traditions of both China and Japan. Monarchs and nobility from these great dynasties often consumed *G. lucidum* as part of special teas and mushroom concoctions. They believed that it could enhance their vitality, promote longevity, and contribute to overall health and well-being (Pan and Lin, 2019). Till date, a great deal of work has been carried out on therapeutic potential of *Ganoderma* (Table 5.1).

Modern thorough investigation on phytochemistry and pharmacology shows that *G. lucidum* basidiocarp, mycelia, and spores contain more than 140 different types of triterpenoids, as well as other compounds such as phenolics, polysaccharides, sterols, nucleotides, fatty acids, proteins/peptides, trace elements, and small-molecular-weight (Mw) proteins (Oke et al., 2022). These compounds are ideal candidates for cosmetics products because they possess antioxidant, anti-ageing, anti-wrinkle, skin-whitening, and moisturizing effects. They also exert numerous biological life span–lengthening activities by inhibiting ROS production, lipid peroxidation, tyrosinase overproduction, acetyl cholinesterase, α-amylase, and α-glucosidase enzymes, increasing production of mitochondrial electron transport complexes, anti-inflammatory, antiproliferative, hepatoprotective, antimicrobial, immunomodulation, anti-atherosclerotic, analgesic, chemo-preventive, antitumor, radioprotective, sleep-promoting, antibacterial, antiviral, hypolipidemic, anti-fibrotic, antidiabetic, anti-androgenic, anti-angiogenic, anti-herpetic, hypoglycemic, estrogenic activity, and anti-ulcer

TABLE 5.1
Effects of Bioactive Components of *Ganoderma* sp. on the Skin

Bioactive Compounds	Biological Effects on the Skin	References
Polysaccharides (several monomers like glucose, mannose, galactose, fucose, xylose, rhamnose, and arabinose)	Antioxidant, antibacterial, anti-ageing, and moisturizing properties on the skin	Sujarit et al. (2021), and Wang et al. (2017)
Terpenoids (ganoderic acids, ganodermanondiol, ganodermanontriol, ganolucidic acids, ganolucidoids, ganoluciduones, lucidadiols, lucidenic acids, lucidumols, methyl ganoderates, and methyl ganolucidates)	Antioxidant, anti-inflammatory, antimicrobial properties on the skin; enhances terpenoid penetration by lowering skin barrier resistance of stratum corneum; and inhibits photoageing	Galappaththi et al. (2023), Baby et al. (2015), Bishop et al. (2015), Grienke et al. (2015), and Nguyen et al. (2015)
Phenolic acids (chlorogenic, cinnamic, gallic, protocatechuic, *p*-hydroxybenzoic, and *p*-coumaric acids)	Antioxidant, antimicrobial, anti-tyrosinase, anti-inflammatory, and anti-ageing properties on the skin	Heleno et al. (2013), Heleno et al. (2012), and Kim et al. (2008)
Tocopherols (alpha and delta isoforms)	Antioxidant properties on the skin, being highly used in clinical dermatology, as photoprotective skin agents against UV radiation	Taofiq et al. (2017)
Vitamin B	Most commonly used in beauty products for the skin, hair, and nails because of their hydrating and anti-ageing benefits	Sheikha (2022)

properties (Yang et al., 2019). However, anti-ageing, anti-tyrosinase, anti-collagenase, anti-elastase, anti-hyaluronidase, and other skin health–promoting effects of *Ganoderma* on human body, along with their modes of actions, remained a closed book to the scientists for a long time (Taofiq et al., 2017). Traditionally, it has been reported that polysaccharides and ganoderic acids are the major functional metabolites of *Ganoderma* which impart its antioxidant and anti-inflammatory functions (Cör Andrejč et al., 2022). Abovementioned bioactivities of *Ganoderma* extracts lead the scientists to investigate on the mechanisms by which the extracts exhibit positive effects on the skin. Modern research unveiled that *Ganoderma* polysaccharides promote skin wound healing, mitigate postburn infection, and prevent skin flap ischemia-reperfusion injury. *Ganoderma* extracts have also been used in skin care, because of their roles in preventing skin photoageing, whitening, hyperpigmentation, and appearances of wrinkles. Also, the anti-inflammatory effect of *Ganoderma* extracts plays a key role in treating atopic dermatitis (AD) and cutaneous sarcoidosis (Figure 5.1) (Yin et al., 2019). Though less explored, these studies and the discussed bioactivities lead the dermatologists and researchers to seek interest in natural cosmetic preparation with *Ganoderma* extracts and to be optimistic about the future of *Ganoderma* and its compounds in the cosmetic industry (Taofiq et al., 2017).

5.6.1 Antioxidant Effect

The oxidative stress is one of the major mechanisms that causes impaired skin structure and function leading to phenotypic features of extrinsic ageing and dermatological conditions. In addition, excessive consumption of alcohol, improper diet, physical inactivity, and mechanical stress can contribute to oxidative damage of skin (Kruk and Duchnik, 2014). Antioxidants are the compounds

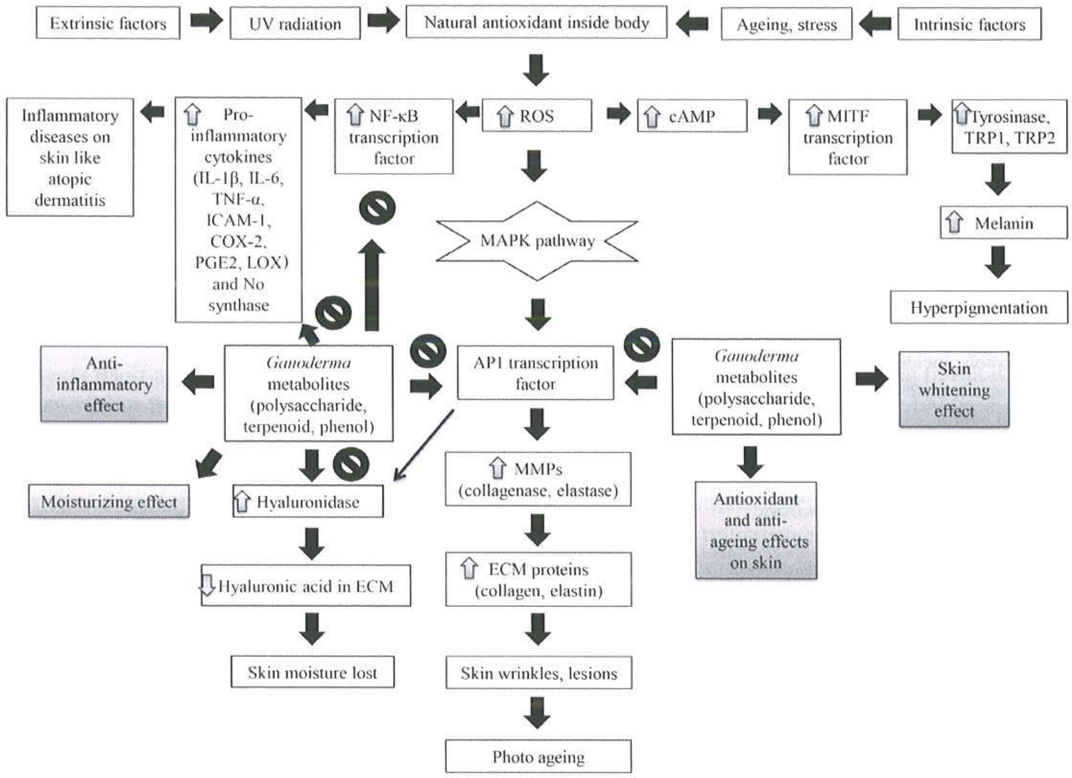

FIGURE 5.1 Overview of anti-ageing effect of *Ganoderma*.

that protect biological system from the deleterious effects of free radicals by neutralizing them (Ribeiro et al., 2015; Khatua and Acharya, 2022). Topically applied antioxidants constitute an important group of pharmacologically active agents capable of preventing the generation of ROS. Free radicals are produced within the body through both endogenous and exogenous pathways. Endogenously, they arise from the normal metabolic processes, where surplus electrons are generated in the mitochondrial respiratory chain. Additionally, inflammation, xanthine oxidase activity, and phagocytosis contribute to the production of free radicals. Exogenously, factors such as smoking, exposure to pollutants, drugs, pesticides, or UV radiation can lead to the non-enzymatic conversion of molecular oxygen into superoxide anion radicals (Oresajo et al., 2012). Human skin is equipped with an array of antioxidants to protect the cells from damaging effects of free radicals, which is of two types: (1) enzymatic antioxidants which are again of two types. One is primary enzymes like glutathione peroxidase, catalase, and superoxide dismutase, which directly inactivate ROS. The other one is secondary enzymes like glutathione reductase and glucose-6-phosphate dehydrogenase, which produce reduced glutathione (antioxidant) from oxidized state and regenerate nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) creating reduced environment, respectively. (2) Nonenzymatic antioxidants include phenols, flavonoids, vitamins (E and C), carotenoids, minerals, and cofactors (Carocho and Ferreira, 2013). These antioxidants slow down the process of ageing either by inhibiting free radicals from oxidizing sensitive biological molecules or by reducing the formation of free radicals and quenching the already-formed ROS (Oresajo et al., 2012).

Serious harm occurs when the balance between production and neutralization of free radicals in the body is lost (Mitra et al., 2021). The levels of these protective antioxidants found in the different layers of the mature skin are greatly reduced with age as well as due to various environmental stresses such as UV exposure leading to various pathological effects in the upper and lower layers of the skin. Cross-linked or glycated proteins are formed due to oxidation of some of the amino acids in susceptible proteins such as collagens and elastin by free radicals. These cross-linked proteins are the classical markers of skin ageing. As one ages, cross-linked proteins in the skin cause stiffening, wrinkling, and awful leathery appearance of the skin (Oresajo et al., 2012). The cascade leads to cellular dysfunction or death and accelerated ageing. ROS induces activator protein-1 (AP-1), a transcription factor that promotes collagen and elastin breakdown in ECM by upregulating enzymes called matrix metalloproteinases (MMPs) which lead to elevated levels of degraded collagen (Leem, 2015). Also, UV radiation causes downregulation of transforming growth factor (TGF-β), a cytokine that promotes procollagen production, thus lowering collagen synthesis (Ansary et al., 2021). Free radicals can directly degrade the sodium hyaluronate present in ECM whose main role is to give a moisturizing effect to the skin and prevent it from oxidative stress. These consequences of free radicals can alter dermal water conservation, tension, elasticity, and softness and are the structural basis of wrinkle formation (Xiang and Jie, 2013). It may also be an essential causative factor for hyperpigmentation or even carcinogenic processes in the skin (Kozarski et al., 2019). Proper ratio of antioxidants in the skin is achieved by topical application or by dietary ingestion that can neutralize ROS and protect the skin from the oxidative stress–induced damages hindering skin ageing. The level of dietary or topical antioxidants achieved in the skin varies with the individual antioxidant and also with absorption and other factors (Oresajo et al., 2012). These important roles of antioxidants in skin health inspired researchers to continuously search for natural compounds capable of scavenging ROS, downregulate MMPs, elastase enzymes, and upregulate TGF-β (Taofiq et al., 2017). In this context, vitamin E (tocopherol) is considered an important antioxidant that is reported to downregulate MMP-1 expression by suppressing AP-1 (Masaki, 2010). Besides, ascorbic acid is usually used in skin care products, but there is a debate in its potentiality due to its inability to penetrate the skin layers together with its poor stability in cosmetic formulations (Boo, 2022).

Till date, many studies have already reported that *Ganoderma* extracts possess strong antioxidant activities. Polysaccharides, one of the primary bioactive components in *Ganoderma* sp., have been demonstrated to encompass various biological properties, such as immune-modulatory, anti-ageing, anti-tumor, and antioxidant activities. A water-soluble, protein-bound polysaccharide with an average Mw of 1013 kDa was isolated from the fruiting bodies of *Ganoderma atrum* which had strong superoxide anion and DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging capacities (Chen et al., 2008). Polysaccharides extracted from *Ganoderma tsugae* by hot water and hot alkali have showed good antioxidant properties (Tseng et al., 2008). Gao et al. (2021) isolated two low-Mw polysaccharides, GLP-1 and GLP-2, from the fruiting bodies of *Ganoderma leucocontextum* which also imparted potent antioxidant properties. The use of *G. lucidum* bioactive extracts in the design of cosmeceutical formulations for topical application is receiving special attention and is investigated by many scientists. Intracellular D-galactose is converted to melampyrin by aldose reductase which becomes deposited in the cells causing alterations in osmotic pressure leading to cellular swelling, dysfunction, metabolic disorders, and finally organism ageing. Studies have portrayed that *G. lucidum* polysaccharide could block the *in vivo* D-galactose–induced skin ageing. Superoxide dismutase exists in human erythrocytes only as CuZn-superoxide dismutase. CuZn-superoxide dismutase mRNA expression and in turn superoxide dismutase activity in human skin are gradually decreased with ageing, which was found to be upregulated by *G. lucidum* polysaccharide (Xiang and Jie, 2013). β-Glucans obtained from wild European *G. lucidum* have shown to enter the stratum corneum and epidermis, penetrating deep into the dermis where they promote collagen synthesis through direct interaction with fibroblasts and via indirect cytokine-mediated interaction with macrophages. As such, β-glucans have been reported to form a thin film above the stratum corneum and epidermis stimulating moisturization (Kozarski et al., 2019). The polysaccharide isolated from *G. lucidum* can improve the ageing process in mice model by increasing the epidermal and dermal thicknesses, superoxide dismutase activity, uniform distribution of dermal collagen fibers, more structural integrity of hair follicles, sweat glands, and sebaceous glands. Alongside, *G. lucidum* polysaccharide can repair the severe oxidative damage which cannot be repaired by vitamin E, indicating the clinical potential for the bio-polymer in ageing (Xiang and Jie, 2013). In another report, Hayati et al. (2020) formulated *Ganoderma* soap containing *G. lucidum* extract in the proportion of 4%–8% and tested its antioxidant potency. They observed that the soap scavenged 50% of free radicals at a concentration of 1.53 mg/mL. Antioxidant activity is one of the major functions provided by triterpenoids and polysaccharides of *G. lucidum*. Reports claim that terpenes such as monoterpenes and sesquiterpenes have the potency to enhance compound penetration across the skin by decreasing the resistance skin barrier of the stratum corneum (Abate et al., 2020). Thus, the content of terpenoids determined for *G. lucidum* can play an important role by enhancing the topical availability of other constituents in cosmeceutical formulations. The existing scientific data are evidence that natural ingredients, especially polysaccharides from *Ganoderma*, can protect the skin from photodamage by neutralizing the deleterious effects of ROS-induced damages, thus lowering skin ageing, and therefore could be applied in cosmeceutical formulations.

5.6.2 Anti-Ageing Activity

5.6.2.1 Anti-Collagenase and Anti-Elastase Activities

The human skin is composed of epidermis, which remains firmly attached and supported by connective tissue to the underlying dermis. Dermal fibroblasts in the ECM generate two structural proteins, namely, collagen and elastin, which are necessary for several protective roles in the skin. Collagen is the most abundant protein in the human dermis layer providing the tensile strength, elasticity, and flexibility of the skin, whereas elastin, a fiber network located in the connective tissue, is responsible for the elastic recoil property (Vaithanomsat et al., 2022).

Progressive age and UV irradiation lead to low levels of both the ECM proteins, i.e. collagen and elastin, mediated through the dermal enzymes like collagenase and elastase, which are zinc-containing MMPs. The alteration causes declined skin resilience as well as skin wrinkling as observed in the case of premature skin ageing and in aged skin (Bae et al., 2008). Besides, UV rays predominately in the UVA range (320–400 nm) act as the main initiator of ROS production (Pillai et al., 2005). The event stimulates mitogen-activated protein kinases (MAPK), which in turn promotes expression of AP-1 leading to uncontrolled expression of MMPs, responsible for collagen and elastin degradation and skin wrinkling. Tissue inhibitors of metalloproteinases (TIMPs) are natural inhibitors disclosed to control unwanted expression of MMPs and further protect the ECM from degradation. Hence, several investigations are being conducted in order to find natural inhibitors of AP-1 as cosmeceutical ingredient to inhibit the expression of MMPs and slow the process of skin ageing (Taofiq et al., 2017; Jiratchayamaethasakul et al., 2020).

Kozarski et al. (2019) screened the anti-collagenase and anti-elastase activities of three different polysaccharide extracts, namely, hot alkali polysaccharide (HWAP), hot-water crude polysaccharide (HWCP), and hot-water polysaccharide purified by dialysis (HWPP), of a wild European source of the mushroom *G. lucidum*. They reported that all the three preparations have the ability to inhibit the two enzymes, but HWCP exhibited the strongest effect as evident by the lowest IC_{50} values (IC_{50}: 0.49 and 1.01 mg extract/mL for collagenase and elastase enzymes, respectively). Additionally, the anti-collagenase and anti-elastase activities of polysaccharides (β-glucan) from antler-type fruiting body of *G. lucidum* were investigated by means of the inhibitions of MMPs, and it was found that the extract inhibited 21.03% and 26.19% of collagenase and elastase, respectively, following substrate competition mechanism where the hydroxyl groups (–OH) of β-glucan competes to bind with the metal ion (Zn^{2+}) of the enzymes, thus preventing the protein to bind with their original substrates (Vaithanomsat et al., 2022).

5.6.2.2 Anti-Hyaluronidase Activity

As mentioned earlier, ECM provides structural and mechanical support to the skin and preserves its integrity and tensile strength (Muiznieks and Keeley, 2013). Degradation of the skin matrix plays a crucial role in the process of skin ageing. Collagen and elastin are structural proteins that are necessary for skin health but are inadequate for a healthy skin matrix. The skin also needs appropriate components to support dermal regeneration, proliferation, and migration. Hyaluronic acid or hyaluronan (HA), a glucose-based polymer, can be commonly found in tissues and fluids of the body, but it is the most bountiful in the dermal compartment of skin and epidermal layer. Hyaluronan mainly promotes skin rejuvenation, contains moisture, increases viscosity, and reduces the permeability of extracellular fluid (Baier Leach et al., 2003). Thanks to its remarkable water-retaining properties, the region rich in HA contributes to emollience, smoothness, and youthful appearance of the skin, all while helping to reduce the appearance of wrinkles. Unfortunately, the level of HA is naturally decreased during the ageing process, leading to loss of moisture due to the synthesis of hyaluronidase enzyme. Hyaluronidase is a group of homologous HA depolymerizing enzymes which plays an important role in the control of size and concentration of HA chains. The protein degrades ECM, resulting in loss of strength, flexibility, and moisture as well as inability of the skin to repair and rejuvenate itself, and subsequently accelerating wrinkle formation and skin ageing. Inhibition of HA degradation thus prolongs the skin moisture by preserving HA contents underneath the skin and is the central to protecting the connective tissues of the skin (Piwowarski et al., 2011; Taofiq et al., 2017; Jiratchayamaethasakul et al., 2020). Till date, several scientists have attempted to screen anti-ageing activity of many *Ganoderma* extracts based on their ability to inhibit hyaluronidase in order to develop anti-ageing cosmetic agents.

Abd Razak et al. (2020) described that the hot-water extract of *G. lucidum* exhibited better anti-hyaluronidase activity than other tested mushrooms such as *Pleurotus ostreatus*, *Auricularia polytricha*, and *Schizophyllum commune* as the fraction inhibited 72.78% of hyaluronidase. In another study, the effects of three mushrooms, namely, *G. applanatum*, *Laetiporus sulphureus*, and *Trametes versicolor*, were determined. The analysis depicted that *G. applanatum* exhibited lesser potency by inhibiting only 1.56% of the enzyme at the highest tested extract concentration of 3 mg/mL. However, the extract from *G. applanatum* presented the highest sun protection factor value (Sułkowska-Ziaja et al., 2021). Furthermore, the anti-hyaluronidase activity of polysaccharides (β-glucan) from antler-type fruiting body of *G. lucidum* was investigated, and it was found that the extract inhibited 29.26% of the enzyme following substrate competition mechanism. The hydroxyl groups (–OH) of β-glucan acted as a substrate analog and competed with binding the metal ion of hyaluronidase, thus preventing the enzyme to bind with HA (Vaithanomsat et al., 2022).

5.6.3 Anti-Inflammatory Activity

The unique role and function of skin is a direct result of its structure and makeup, particularly of the most superficial part, the epidermis. The main cellular component of the epidermis includes keratinocytes which possess all inflammasome components and are produced as a series of protective as well as regenerative responses of the body. Therefore, inflammation in the skin is a physiological response, characterized by redness, swelling, itching, and pain, and it either occurs as a result of tissue injuries, autoimmune responses, and immune responses against infections, or is hereditary (Dawid-Pać, 2013; Lin et al., 2017). Under the influence of inflammatory factors, monocytes and macrophages produce several cytokines which in turn activate cells involved in inflammation like neutrophils, macrophages, and mast cells; induce the prostaglandin synthesis; and affect the synthesis of C-reactive proteins. Chronic inflammatory responses occur as a result of overproduction of pro-inflammatory mediators such as interleukins (IL)-1β, IL-6, IL-8, inducible-type cyclooxygenase-2 (COX-2), tumor necrosis factor (TNF-α), 5-lipoxygenase (5-LOX), nuclear factor (NF)-κB, prostaglandin E2 (PGE2), intercellular adhesion molecule-1 (ICAM-1), and inducible nitric oxide synthase (iNOS). In the case of skin inflammation, disturbance in the synthesis of eicosanoids occurs in epidermal cells, resulting increased production of neurological mediators like P substances that consequently stimulate nitrogen oxide production (Dawid-Pać, 2013; Taofiq et al., 2017).

One of the typical chronic inflammation-based skin diseases is AD, also known as atopic eczema, characterized by intense itch, recurrent eczematous lesions, and pruritic skin lesions with complex etiology caused mainly by overactive immune response, genetic factors, and influence from environment (Weidinger et al., 2018). Early clinical signs of AD include excessive skin dryness, itching, exfoliation, roughness and pruritus, redness, exudations, swelling of the affected skin areas, spots, rash, and blisters with watery secretion. AD is distinguished by invasive leukocytes, dysfunctionality in stratum corneum, altered expression of epidermal differentiation genes (e.g., loricrin- and proline-rich region proteins), and decreased water retention capacity. Pathogenesis of AD is attributed to the enhanced histamine release, elevated serum immunoglobulin E (IgE) levels, and sensitization to a variety of inhalant, food and microbial allergen, activation of T lymphocytes, epidermal barrier dysfunction, and chronic Th2-related cytokines production within the skin (David et al., 2017). Skin cells produce IL, prostaglandin, and proteases initiating inflammatory reactions. Skin dryness, a characteristic of AD, is caused primarily by increase in trans-epidermal water loss which is related to lowered lipid concentration (especially ceramides) in epidermal cells and loss of factors of NMF. Loss of function mutation of fillagrin (FLG) gene also contributes to impaired skin barrier function. Besides, Th2-related cytokines (IL-4) worsen the skin barrier impairment by modifying the keratinocyte differentiation and lipid synthesis of the intercellular compartment of the stratum corneum (Dawid-Pać, 2013; De Benedetto et al., 2015; Lin et al., 2017; Taofiq et al., 2017; Luger et al., 2021). NF-κB, a transcription factor, regulates the expression of several pro-inflammatory cytokines and enzymes such as IL-1β, TNF-α, iNOS, and COX-2. Hence, search for natural inhibitors of one or two steps in the NF-κB pathway is critical for preventing inflammation-related disorders (Taofiq et al., 2017).

So far, numerous investigations have reported that bioactive compounds of *Ganoderma* such as polysaccharides, terpenes, phenolic compounds, steroids, and other metabolites exhibit anti-inflammatory potential based on their ability to reduce the production of inflammatory mediators. The mode of action has been assigned to the reduced expression of inflammatory mediators, for instance, NO, IL-1β, IL-6, IL-8, TNF-α, and PGE2 (Wu et al., 2019; Su et al., 2020). In a clinical trial, five patients suffering from AD were subjected to oral administration of four *G. lucidum* tablets in divided doses per day containing extract equivalent to 0.94 g of dried mushroom each. It was observed that there was a marked attenuation in severity scores, serum IgE levels, thymus, and activated-regulated chemokine (TARC) with improved clinical symptoms indicating potential application of the mushroom (Michio and Masato, 2015).

Cutaneous sarcoidosis is a systemic inflammatory disease characterized by the pathological development of noncaseating epithelioid granulomas, multiple plaques lesions, granulomas consisting of epithelioid histiocytes, and multinucleated giant cells. In a case report, a 44-year-old male patient had suffered from annular cutaneous sarcoidosis on his scalp for 4 years. The multiple plaque lesions almost disappeared by the topical application of Ganosoap (*G. lucidum* with the goat milk) foam on the lesion for 1 h, and then rinsing it and repeating the procedure for a total of 3 days (Saylam Kurtipek et al., 2016). Topical application of the ethanolic extract of *G. lucidum* 30 min prior to croton oil application markedly inhibited the skin inflammation in mouse (Lakshmi et al., 2003). Hence, the prevalent researches confirmed that several biomolecules from *Ganoderma* treated inflammatory skin diseases by both topical and oral applications, indicating the fact that this fungus could be used to formulate cosmeceuticals, nutricosmetics, emollients, ointments, and so forth.

5.6.4 Antimicrobial Activity

The skin is a living and active tissue that acts as a barrier by preventing entry of pathogens into the body. It also acts as a part of the adaptive immune system. Therefore, the anatomical and physiological health of the skin tissue is vital for human immunity (Kabashima et al., 2019). The skin is exposed to a large volume of beneficial microorganisms every day based on its anatomical position in the body. Among the most common ones include *Corynebacterium*, *Bacillus*, *Klebsiella*, *Micrococcus*, *Pseudomonas*, *Propionibacterium*, *Staphylococcus*, and some of the *Acinetobacter* sp., which are the important microbes isolated from the skin. Common skin diseases caused by fungi that colonize skin tissue are due to *Candida* and *Tinea* sp. Distribution and density of the skin microflora depend on the individual's age and environmental factors such as sebum secretion, temperature, and humidity. A balance between the physical structures and biological parameters of the skin is thus necessary to maintain the skin health, and any imbalance in this equation can lead to severe skin disorders or infections (Kloos and Musselwhite, 1975; Grice et al., 2009). Some of the most common clinical forms of these infections are known to cause inflammatory skin diseases such as AD, seborrheic dermatitis, cellulitis, erysipelas, impetigo, folliculitis, furuncle, carbuncle abscess, folliculitis, and psoriasis (Ujiie et al., 2022). Among the aforementioned skin diseases, AD has been known to be linked with increased colonization of the skin by microbes such as *Staphylococcus aureus*, and these organisms tend to exacerbate the intensity of the disease (Salah and Faergemann, 2015). Cosmetic and pharmaceutical industries are constantly looking for interesting bioactive compounds of natural origin to replace synthetic antimicrobial agents in topical products coupled with the fact that these bacteria also develop resistance against conventional topical antimicrobials due to their continuous application for long term (Ribeiro et al., 2015).

A great deal of scientific studies so far has reported the antimicrobial potential of many species of *Ganoderma* as well as their bioactive compounds (Taofiq et al., 2017). Indeed, herbalists usually consider *Ganoderma* as a natural regulator of immune system maintaining it at optimal levels. The local traditional doctors of south-western Nigeria have used *Ganoderma* sp. in the treatment of various skin disorders (Jonathan and Awotona, 2010). In a research work, four different types of solvents (hexane, chloroform, dichloromethane, and methanol) were used to screen the antimicrobial potential of *Ganoderma boninense* fruiting bodies against some common skin diseases caused by bacterial pathogens such as *Bacillus subtilis*, *Bacillus cereus*, *Escherichia coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, *Streptococcus pneumonia*, and *S. aureus* using disc diffusion assay. Most of the extracts exhibited some extent of inhibition to both Gram-negative and Gram-positive bacteria. However, the activity was more pronounced against the Gram-positive bacteria, whereas around 66.7% inhibitory effect was recorded against Gram-negative microbes. It could be justified by the presence of lipopolysaccharide in their outer wall of Gram-negative bacteria which may help them become more resistance to the extracts (Ismail et al., 2014). In another report, Hayati et al. (2020) formulated *Ganoderma* soap containing *G. lucidum* extract in the proportion of 4%–8% and tested its antimicrobial potency against one Gram-positive (*S. aureus*) and two Gram-negative bacteria (*E. coli*, *P. aeruginosa*), and one fungus (*Candida albicans*) using agar well diffusion method. They reported that the product exhibited potent antibacterial effect against all the strains to some extent using 10% soap. Comparatively, *S. aureus* appeared as the most susceptible and *C. albicans* was detected as the most resistant among all the microbial strains investigated in the work. However, *Ganoderma* transparent soap was found to be inactive against *P. aeruginosa* and *C. albicans* at a concentration level of 1%. This research thus indicated that *G. lucidum* extract could be formulated as a transparent soap to add its functionality.

5.6.5 Anti-Tyrosinase Activity

Melanin is a black pigment synthesized from tyrosine by epidermal melanocytes, responsible for the color of the eyes, hair, and skin. It is produced and secreted through a physiological process, called melanogenesis, by the melanocytes which are distributed in the basal layer of the dermis (Maranduca et al., 2019). There are two types of melanin pigments produced by the melanocytes such as eumelanin (black or brown) and pheomelanin (red or yellow). The color of human skin and hair is determined by the type and distribution of the pigment. Melanin protects the skin against UV damage by absorbing the light and removing ROS or by transferring melanin to adjacent keratinocytes. Overexposure of the body to UV radiation causes excessive synthesis of melanin in the skin, due to the amplified activity of tyrosinase. Tyrosinase (EC 1.14.18.1), a polyphenol oxidase and the rate-limiting enzyme, can orchestrate two distinct reactions in melanin biosynthesis pathway: conversion of tyrosine to L-dihydroxyphenylalanine (L-DOPA), and oxidation of it into dopaquinone (Meng et al., 2014). This compound is converted to either dopachrome through auto-oxidation which in turn is converted to eumelanin (brown-black pigment) in the presence of dopachrome tautomerase or is converted to cysteinyl DOPA in the presence of cysteine or glutathione to form pheomelanin (yellow red pigment) (Liu, 2022). Abnormal accumulation and biosynthesis of melanin pigments are responsible for skin hyperpigmentation disorders such as melasma, freckles, and senile lentigo (Ribeiro et al., 2015). Hyperpigmentation disorders are unpleasing abnormalities usually distinguished by darker skin appearance, light to dark brown spots, irregular gray patches on the face, neck, and trunk, and pale brown to dark brown spots on the skin having a significant impact on external appearance, leading to psychological and emotional distress and reduction in the quality of life of affected patients. The main causes of skin hyperpigmentation include autoimmune conditions, exposure to UV radiation, hormonal changes causing release of α-melanocyte-stimulating hormone, genetic factors, hormonal therapy or birth control pills, and medication causing drug reaction. All these factors trigger oversecretion of melanin from melanocytes causing hyperpigmentation (Ali and Naaz, 2015). Several signal transduction pathways are responsible for the upregulated melanin production mediated through expression of tyrosinase, tyrosinase-related protein 1, and tyrosinase-related protein 2 (Chang, 2012). Melanogenesis is initiated by several hormonal and chemical mediators, the most common of which is cAMP-mediated pathway (Meng et al., 2014). cAMP is reported to increase the expression of microphthalmia-associated transcription factor via activation of cAMP-dependent protein kinase A and cAMP-response element binding protein transcription factor. The complex melanogenesis process is controlled by activity of microphthalmia-associated transcription factor (MITF), which binds to the promoter region of tyrosinase-related proteins, tyrosinase-related proteins 1 and 2 thereby causing overexpression of tyrosinase responsible for melanin biosynthesis (Park et al., 2011). Hence, compounds that tend to cause inhibition of MITF expression or can reduce the catalytic activity of tyrosinase, thus hindering melanin synthesis, transfer, and deposition, will be an inhibitor to the whole process of melanogenesis. It eventually leads to the decrease of total melanin production, which will be a therapeutic approach for combating skin hyperpigmentation (Gillbro and Olsson, 2011).

"Lingzhi" is a common name in various cosmetic compositions and may contribute to the whitening of skin. This property is highly valued by many oriental (Chinese and Japanese) women. In 2008, it was elucidated for the first time that 75% and 50% ethanolic extracts as well as water extract of *G. lucidum* inhibited about 80% of tyrosinase activity at a concentration of 1 mg/mL (IC_{50}: 0.32 mg/mL) among the tested Basidiomycetes (*Cordyceps militaris*, *Agaricus brasiliensis*, and *Antrodia camphorata*) (Chien et al., 2008). In another work, ganodermanondiol, an extract prepared from *G. lucidum*, was reported to affect the melanin production by decreasing the expression of tyrosinase-related protein 1, tyrosinase-related protein 2, and MITF in B16F10 melanoma cells. Moreover, the treatment of ganodermanondiol at 10 μM could increase phosphorylation of ERK and JNK, and suppress phosphorylation of p38, suggesting that the fraction may inhibit melanogenesis by modulating MAPK signaling pathways. Until 2016, the de-pigmenting effects of *Ganoderma* ingredients on an animal model had not been investigated. Hsu et al. (2016) found that 200 ppm of the ethyl acetate fraction of *Ganoderma formosanum* (ATCC 76537) mycelia ethanolic extract not only reduced approximately 50% of melanin formation of zebrafish embryos but also exhibited better de-pigmenting activity than that of kojic acid, a standard de-pigmenting drug. Sułkowska-Ziaja et al. (2021) determined the anti-tyrosinase activity of three mushrooms, namely, *G. applanatum*, *Laetiporus sulphureus*, and *Trametes versicolor*, and reported that *G. applanatum* exhibited a dose-dependent increase in its potency by inhibiting about 66.74% of tyrosinase at the highest tested extract concentration, i.e. 3 mg/mL. Despite the thorough *in vitro* characterization of the mechanisms of these inhibitors, they have not been utilized topically in cosmetics and cosmeceuticals. Therefore, additional assessment of their skin-whitening activity is necessary through *in vivo* studies or concurrent human clinical trials.

5.6.6 Anti-Melanoma Effect

Melanoma is one of the most aggressive metastatic of skin cancer accounting for 80% of skin cancer-related deaths worldwide (Dhanyamraju and Patel, 2022). It is one of the most aggressive and lethal kinds of skin cancer, originating from melanocytes situated at basal layers of epithelial surface. Melanoma development depends on the number of melanocytic nevi, mutagenesis, genetic vulnerability, and exposure to UV radiation, imparting genotoxic outcome. The present therapies comprise immune-therapy, surgical resection, radiotherapy, and chemotherapy; nevertheless, these are only fruitful during less invasive and early-stage melanoma (Dhanyamraju and Patel, 2022). Hence, improvement of therapeutic agents for melanoma is an urgent need where nature-derived products could be a critical source being considered as lesser toxic than synthetic drugs.

Researchers have shown that *G. lucidum* polysaccharide at a concentration of 40 μg/mL could antagonize UVB-induced melanogenesis by downregulating the expression of genes such as MITF, tyrosine, tyrosinase-related proteins 1 and 2, and Ras-related protein Rab27A and inhibiting cAMP/PKA and ROS/MAPK signaling pathways suggesting potential use of *G. lucidum* polysaccharide as a natural, safe whitening and sunscreen agent (Hu et al., 2019). It has been reported by Jiang et al. (2019) that *G. lucidum* polysaccharide could affect melanogenesis in melanocytes through regulating paracrine mediators secreted by keratinocytes and fibroblasts. Human skin pigmentation is regulated by complex and intricate interactions between melanocytes and keratinocytes in the epidermis and fibroblasts in the dermis. *Ganoderma lucidum* polysaccharide, when used at concentrations of 2.5, 5, and 20 μg/mL, has been shown to markedly inhibit several paracrine factors secreted by keratinocytes and/or fibroblasts. These factors, including proopiomelanocortin-derived hormones, typically stimulate melanocytes, leading to an increase in melanogenesis and subsequent skin hyperpigmentation. The inhibition occurs at the transcriptional level, resulting in the deactivation of the MAPK pathway in PIG1 melanocyte cells. This indicates that *G. lucidum* polysaccharide may serve as a practical agent for preventing pigmentation by exerting a skin-whitening effect. Shin et al. (2021) demonstrated that lucidadiol, a triterpenoid isolated from *G. lucidum*, could exert anticancer activity against B16 melanoma cells via inducing apoptosis mediated through the Akt/MAPK pathway. Similar anti-metastatic potential has been reported by Barbieri et al. (2017) where *G. lucidum* extracts inhibited the viability of B16-F10 cell line, suggesting application of the fractions for therapeutic management of melanoma. Another research suggested that *G. lucidum* polysaccharide-peptide had an antitumor metastatic activity under sleep fragmentation condition. Collectively, the compound affected proteomic profile, macrophage polarization, gut microbiota constituents, and TNF-α synthesis in mice bearing B16-F10-luc-G5 with SF (Xian et al., 2021). Recently, 9,11-dehydroergosterol peroxide [9(11)-DHEP], an important steroid isolated from submerged culture of *G. lucidum*, was subjected to the malignant melanoma cells to understand antitumor effect. Results showed that the compound was able to inhibit the growth of A375 human malignant melanoma cells via downregulation of induced myeloid leukemia cell differentiation protein Mcl-1. Similarly, Lu et al. (2019) revealed that ketoconazole, an antifungal agent, enhanced the ability of immunomodulatory proteins of *Ganoderma microsporum* to inhibit proliferation and migration of A375.S2 melanoma cancer cells, and hinder expression of monocyte chemo-attractant protein 1 (MCP-1).

5.6.7 Wound-Healing Activity

A wound damages the skin barrier resulting in microbial invasion and inflammation. Cutaneous wound healing is a complex sequence of cellular and molecular processes by which skin repairs itself. Regarding cellular mechanism of the wound-healing process, tremendous progress has been made in recent years in identifying the critical events responsible for wound healing. In brief, there are four stages of the wound-healing process: (1) hemostasis which occurs at the wound site and requires platelets to repair damaged blood vessels through the process of blood clotting; (2) inflammation which is carried out by neutrophils and macrophages in response to tissue injury via cytokine release and phagocytosis; (3) proliferation which starts approximately at the fourth day after wounding marked by the involvement of specialized fibroblast cells secreting various enzymes that degrade the fibrin clot, and then replace it with ECM components (such as collagen and hyaluronic acid); and (4) tissue remodeling which is an essential stage in returning the injured tissue to a state similar to that before injury involves realignment of the collagen tissue (Guo and Dipietro, 2010). Moreover, within the epidermal layer, keratinocytes play a pivotal role in the reepithelialization process of the stratum corneum, which contributes to the regeneration of the epidermis. Additionally, keratinocytes are involved in wound contraction, further facilitating the healing process of the skin. In humans, keratinocytes reform a functional epidermis (reepithelialization) as rapidly as possible, closing the wound and re-establishing tissue homeostasis. Though regular wound-healing process can occur spontaneously, many internal and external factors can interfere with the progression causing an ultimate delay of wound repair. Dysregulation in any phase of the cascade not only delays healing but may also result in various skin pathologies, including non-healing or chronic ulceration. Therefore, an attempt to identify remedies that could successfully accelerate skin wound healing would be of significant interest.

In this context, Montalbano (2018) advocated that *G. lucidum* could be used to treat chronic non-healing wounds *in vitro*. Nanogel-containing triterpenoids isolated from the taxon have exhibited favorable effects on the frostbite-healing process by increasing the wound-healing area and improving the degree of pathological change in skin tissue of rats with frostbite (Shen et al., 2016). In another study, *G. lucidum* polysaccharides promoted migration ability of fibroblasts and upregulated the expressions of C-terminal peptide of procollagen type I and transforming growth factor-β1 in fibroblasts resulting in wound healing (Hu et al., 2019). Moreover, the topical application of 10% w/w polysaccharide-rich extract derived from *G. lucidum* could enhance wound healing in streptozotocin-induced diabetic rats with improved blood circulation providing more oxygen and nutrients essential for the healing process. The mode of action was mediated through the upregulation of collagen synthesis and angiogenesis at the wound site (Cheng et al., 2013). Sacchachitin membrane, an alternative of weavable skin, that was prepared from the residual mass obtained during solid-state cultivation of *G. tsugae* has been exhibited to promote skin wound healing (Hung et al., 2001). Topical gel preparations of the combination of *Ganoderma praelongum* and *Glycyrrhiza glabra* aqueous extracts remarkably increased the wound contraction in excision wound and shortened the period of epithelialization to nearly by 2 days (Ameri et al., 2013). Additionally, Krupodorova et al. (2015) investigated for skin wound-healing activity *in vivo* using the excision wound-healing model where 100 mg/1 mL of *Crinipellis schevczenkovi* and *G. lucidum* extract was applied to white albino male mice. In the case of topical application on the fifth day, the wound-healing effects of both mushroom extracts were almost at the same level and better than the results in the control group. The wounds were completely covered on the sixth day compared with the eighth day in the control group. The research thus indicated that *Ganoderma* extract alone or in combination with other preparations can fasten up the skin wound-healing process when applied topically, suggesting that the mushroom could be further investigated and marketed as ointments and balm for medical use.

5.7 COMMERCIALLY AVAILABLE COSMETICS WITH *GANODERMA*-BASED INGREDIENTS

Recently, the cosmetic industry is in a constant search for valuable bioingredients with anti-ageing (antioxidant, anti-inflammatory, anti-tyrosinase, anti-collagenase, anti-elastase, anti-hyaluronidase, and wound-healing) properties. Edible and medicinal Agaricomycetes mushrooms (macrofungi) are packed with an unlimited source of bioactive compounds having a wide range of medicinal properties. Nowadays, they have also been included in cosmetic formulations for topical and oral administration (Badalyan et al., 2022). However, the safety is a vital reason for its prevalence where *G. lucidum* has presented no toxicity to human fibroblast cells *in vitro* and *in vivo* justifying it as a safe and effective medical and healthcare agent. For instance, ethanolic soxhlet extracts of *G. lucidum* were evaluated for antioxidant, anti-inflammatory, anti-tyrosinase, antimicrobial, and cytotoxic effects, and the obtained fractions were tested as cosmeceutical ingredients. The developed formulation was found to preserve the extract bioactivities, presented a light yellow color and pH of 4.6, which is considered appropriate for the design of a cosmeceutical. However, more *in vivo* and clinical studies are necessary in order to develop and validate novel nutraceuticals, cosmeceuticals, and pharmacological formulations (Taofiq et al., 2017).

The relevance of *G. lucidum* properties is evident from the number of commercial cosmeceutical products in the market formulated from their extracts, either alone or in combination with other natural ingredients. Dr. Andrew Weil (https://www.origins.com/dr-weil-mega-mushroom), launched in 2006, was among the first premium Western brands to exploit fungi in skin care. The product is a skin relief face mask used to calm, sooth, and defend skin against visible signs of ageing. Its formulation includes mycelium of *Hypsizygus ulmarius* and extracts of *G. lucidum* and *Ophiocordyceps sinensis*. Menard is a brand of cosmetic product with mushroom ingredients (www.menard-cosmetic.com) which employs *G. lucidum* extract in its Embellir range, not only to suppress the severity of hyperpigmentation and enhance skin glow, but also to eliminate toxins and help repair skin damage associated with excess exposure to free radicals and UV radiation. Estée Lauder incorporated *G. lucidum*, wolfberry, and ginseng, along with additional antioxidants, moisturizers, cell-communicating ingredients, and blends of common skin ingredients in a novel Re-Nutriv sun care product (www.esteelauder.com). Currently, *G. lucidum* extracts have been commercially used in a variety of facial mask cosmetics as a kind of tyrosinase inhibitors (Table 5.2). These products claim to revive the skin radiance and help reduce the ageing effects due to daily exposure to UV radiation, including formation of age spots, uneven skin tone, and other imperfections (Taofiq et al., 2017).

TABLE 5.2
Use of *Ganoderma* in Different Cosmetic Products

Product	Function	References
Eminence Organic Skin Care Birch Water Purifying Essence	Anti-ageing and provides hydration	https://eminenceorganics.com
Yves Saint Laurent Temps Majeur Elixir De Nuit	Anti-ageing	https://www.yslbeautyus.com
Dr. Andrew Weil for Origins™ Mega-Mushroom Skin Relief Micellar Cleanser	Anti-ageing	https://www.origins.com
Shiseido: Ultimune Power Infusing Concentrate	Anti-ageing and anti-inflammatory	https://www.shiseido.com

(Continued)

TABLE 5.2 (*Continued*)
Use of *Ganoderma* in Different Cosmetic Products

Product	Function	References
Tela Beauty Organics Encore Dri Styling Cream	Hair protection from sun damage and color fading	https://www.nordstrom.com
DXN Ganozhi E Nourishing Night Cream, UK	Improves firmness while strengthening the skin's structure	Wu et al. (2016)
DXN Ganozhi E Hydrosoft Toner, UK	Cleanses and minimizes pores, penetrates, and tones skin	www.ganodermalucidumproducts.com
DXN Ganozhi E UV defense Day Cream, UK	Hydrates, firms, moisturizes, and protects against UV rays	www.ganodermalucidumproducts.com
DXN Ganozhi Moisturizing Micro Emulsion, Malaysia	Hydrates and nourishes the skin	www.ganodermalucidumproducts.com
DXN Ganozhi Lipstick, Malaysia	Hydrates the lips with a natural, subtle shine	www.dxnmalaysia.com
Guangzhou Maycare cosmetics, Collagen crystal facial mask, China	Skin revitalizing and whitening	Taofiq et al. (2017)
Guangzhou Bocaly Bio-Tec., *Ganoderma* Cells Repairing Anti-ageing Face Mask, China	Anti-wrinkle, firming, lightening, moisturizer, nourishing, pigmentation correctors, pore cleaner, and whitening	www.may-care.com
Julie Levin Organic skin Care, Green Tea Reishi Face Serum, US	Nourishes and invigorates the skin	Hyde et al. (2010)
Kat Burki Form Control Marine Collagen, Gel, U.K.	Boosts collagen, improve elasticity, and provide hydration	www.leafpeople.com
MAVEX, 24 h Intensive Cream, Hong Kong	Stimulates cell turnover formation of collagen and elastin, and skin anti-ageing	Wu et al. (2016)
MAVEX, Rejuvenating Treatment, Hong Kong	Antioxidant action and deep cellular renewal. Fights degenerative processes and the negative action of free radicals	www.dazzlinggroup.com
MAVEX, Hyaluronic Lifting Serum, Hong Kong	Stimulates collagen synthesis and keeps the skin toned, hydrated, and luminous, and skin anti-ageing	www.dazzlinggroup.com
MAVEX, Beauty Secret Eye Contour, Hong Kong	Skin anti-ageing, anti-edema, prevents and reduces edemas, and fights the formation of wrinkles	www.dazzlinggroup.com
MAVEX, 2 in 1 Cleansing Milk & Tonic, Hong Kong	Effectively removes impurities and residues of makeup, deeply purifies, deeply protects, and moisturizes the skin	www.dazzlinggroup.com
MAVEX, AHA/BHA Peeling, Hong Kong	Effective exfoliates keratolytic and bio-stimulating properties, and skin anti-ageing and revitalizes	www.dazzlinggroup.com
Paris Skin Institute, Derma Sublime, Luxurious Revitalizing crème, France	Intensely hydrates and comforts dry and sensitive skin	www.dazzlinggroup.com

(Continued)

TABLE 5.2 (*Continued*)
Use of *Ganoderma* in Different Cosmetic Products

Product	Function	References
Shenzhen Hai Li Xuan Technology, HailiCare Skin-Whitening Cream, China	Removing freckle speckle and whitening	Hyde et al. (2010)
Yves Saint Laurent Temps Majeur Elixir De Nuit, France	Anti-ageing	Wu et al. (2016)
Nanjing Zhongke Pharmaceuticals, *Ganoderma* Face Cream Set (Day/night cream and eye gel set), China	Immunity booster and anti-fatigue	Hyde et al. (2010)
Nano Works Shineluxe (*Ganoderma lucidum, Lentinula edodes, Mucor miehei*)	Anti-ageing	www.coracosmetics.com

5.8 CONCLUSION AND FUTURE PERSPECTIVES

The present review underscores the remarkable potential of *Ganoderma* sp. in revolutionizing the field of skin healthcare. The amalgamation of traditional knowledge with contemporary scientific evidence highlights multifaceted contributions of the genus *Ganoderma* to skin health, ranging from its antioxidant, anti-inflammatory, antimicrobial, anti-tyrosinase, anti-hyaluronidase, anti-elastase and anti-collagenase properties to its capacity for enhancing collagen synthesis and moisture retention. The promising results from *in vitro* and *in vivo* studies pave the way for innovative skincare formulations and therapeutic interventions. However, while the existing body of research is promising, several avenues for future exploration and development in *Ganoderma*-based skincare still remain. First, more clinical trials are essential to validate the efficacy and safety of *Ganoderma* extracts across diverse skin types and conditions. This could be a pivotal factor in the effective formulation of cosmetic ingredients designed to shield and fortify the skin against free radicals. These ingredients may work to diminish the production of inflammatory mediators and impede collagenase, elastase, and tyrosinase associated with inflammatory conditions, wrinkles, aging, and hyperpigmentation. Rigorous investigations should elucidate optimal concentrations and delivery mechanisms to ensure maximal benefits. Furthermore, deeper mechanistic studies are required to unravel the precise pathways through which *Ganoderma* influences skin health. This could facilitate the targeted design of skincare products tailored to specific dermatological concerns. Additionally, exploring synergistic effects between *Ganoderma* and other natural or synthetic skincare ingredients could yield novel formulations with enhanced therapeutic potential. The integration of *Ganoderma* into personalized skincare regimens also presents an exciting avenue. Leveraging advances in genomics and skin microbiome research could enable the customization of *Ganoderma*-based treatments based on individual genetic and microbial profiles. In summary, *Ganoderma* holds immense promise as a transformative agent in skincare. By bridging traditional wisdom with contemporary scientific insights, its potential to address a spectrum of skin health issues is evident. As the field of skincare continues to evolve, further research and innovation in *Ganoderma*-based interventions are poised to reshape the landscape of dermatological care, offering safe, effective, and nature-inspired solutions for diverse skin-related challenges.

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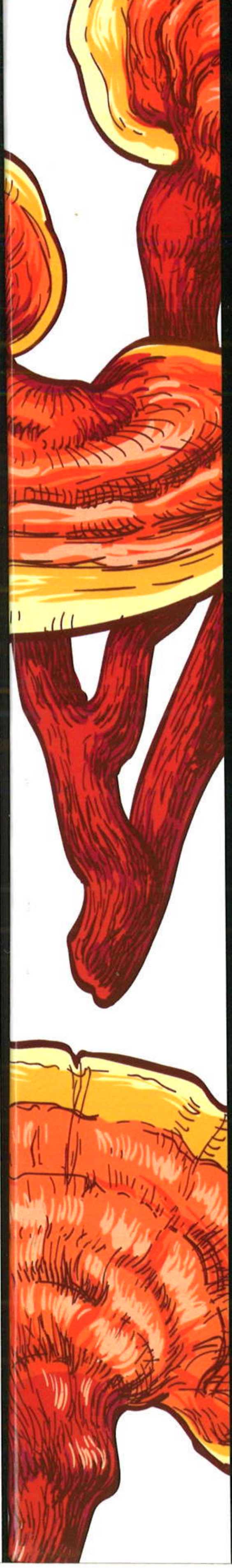

For the past two millennia, *Ganoderma* has been prized as the "mushroom of immortality" in ancient Asian cultures, owing to its health benefits. Modern research has further revealed that the genus is rich in bioactive components, including polysaccharides and triterpenoids, uncovering various medicinal prospects both *in vitro* and *in vivo*. Clinical trials conducted so far have emphasized the safe and effective use of the mushrooms, with a particular focus on *Ganoderma lucidum*. Currently, the *Ganoderma*-based industry is witnessing a significant surge, offering a plethora of dietary and medicinal products. Recognizing the impact of these developments, the book *Ganoderma: Cultivation, Chemistry, and Medicinal Applications Volume 2* aims to consolidate the latest information on the macrofungi, emphasizing its bioactive compounds, diverse therapeutic effects, and industrial applications.

Key Features:

- This book provides a thorough exploration of *Ganoderma* polysaccharides, unraveling their chemical composition, structure, and potential health benefits.
- Comprehensive coverage is provided to understand antimicrobial properties of the medicinal mushrooms. The text also delves into the potential role of *Ganoderma* in safeguarding against various skin diseases, accompanied by discussions on underlying mechanisms.
- A detailed examination of *Ganoderma* includes its potential cardioprotective effects, encompassing impacts on blood pressure, cholesterol level, and overall heart function. This book also provides an in-depth analysis of the capacity of the macrofungi to stimulate the immune system.
- The volume encompasses findings related to the impact of *Ganoderma* on prevention or mitigation of neurodegenerative diseases.
- Additionally, it contributes to the understanding of medicinal applications by exploring *Ganoderma*-based nanoparticles, offering novel insights into potential therapeutic avenues.
- A comprehensive overview of the *Ganoderma*-inspired industry highlights its diverse contributions ranging from dietary supplements, cosmeceuticals, and nutricosmetics to healthcare products.

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