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The Sugar Coated Killer *Cryptococcus neoformans*: New Insights into Its Polysaccharide Capsule

Forman Erwin Siagian [a*]

[a] *Department of Parasitology, Faculty of Medicine, Universitas Kristen Indonesia, Jakarta, Indonesia.*

Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

Aims: To analyze the polysaccharide property of capsular portion belongs to the incidiosa yeast, *Cryptococcus neoformans*.
Discussion: *Cryptococcus neoformans* is an encapsulated fungal pathogen that is acquired by human and animal hosts through inhalation of environmental infectious propagules and can stay dormant or minimally parasitized in the lung alveoli. It is lethal to the immunocompromised individuals, especially HIV (+), which can have caused cryptococcal meningitis. Morphologically, it is a round or oval-shaped yeast cell. The size of the organism is ~2.5 µm without the capsular polysaccharide. The capsule is found immediately outside the cell wall and can vary in size from 1 to 50 µm, depending on the cell type, environment, and growth conditions. Capsule architecture is characterized by a complex Biochemical network connected to the cell wall and extending to variable distances into the extracellular space. The capsular portion of *C. neoformans* is always considered as the primary virulence factor. From the Biochemical properties, it is primarily composed of polysaccharides, most notably glucuronoxylomannan (GXM) and to a lesser extent, galactoxylomannan (GalXM), and mannoproteins. This elastic and thick, hydrophilic capsule is

**Corresponding author: E-mail: forman.siagian@uki.ac.id;*

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essential for the fungus's ability to cause disease, as it protects the yeast from the host's immune system by hindering phagocytosis and by modulating the phagosome environment. *Cryptococcus* cells from clinical samples typically have a much thicker capsule than those from the environmental samples or from culture medium. Fortunately, as a surprising findings, this capsular polysaccharide can be used as a simple methods of detection through the cryptococcal antigen in diagnostic tests.
Conclusion: In *C. neoformans*, the components of the capsular network constitute the main fungal virulence factor as well as a precious element for simple detection.

Keywords: Yeast; opportunistic; parasitic; Macromolecules; Glucuronoxylomannan (GXM); Galactoxylomannan (GalXM); β-glucans; mannoproteins; neglected tropical diseases.

1. INTRODUCTION

Cryptococcus phylogeny reveals a complex genus with closely related pathogenic species (Coelho et al., 2025; Montoya, et al., 2025; Chen et al., 2019), such as *C. neoformans* (Ashton, et al., 2019) and *C. gattii* (Hitchcock & Xu, 2023) that are grouped into a pathogenic "clade" within the Tremellales order (Bahn, et al., 2020). Within these species, distinct molecular types exist, like VNI, VNII, VNB, VNIII, VNIV (for *C. neoformans*) and VGI, VGII, VGIII, VGIV and VGV (for *C. gattii*) (Farrer et al., 2019; Cogliati 2013). "Phylogenetic studies conducted by Ashton et al revealed that a recent exponential population expansion, consistent with the increase in the number of susceptible hosts. In our study population, this expansion has been driven by three sub-clades of the *C. neoformans* VNIa lineage; VNIa-4, VNIa-5 and VNIa-93" (Ashton, et al., 2019). "This finding also highlight a recent and rapid population expansion in *C. neoformans*, driven by specific lineages, and uncover novel species and diversity within the genus. The fungal species in the Tremellales are numerous, representing over 120 species, and many of their phylogenetic relationships are weakly supported due to the lack of multilocus phylogenetic and phenotypic analyses" (Findley et al., 2009). However, the next part of this article will be focuses only on *C. neoformans*.

"Cryptococcus neoformans is an opportunistic fungal pathogen that can cause a severe and potentially fatal infection called cryptococcosis, primarily in individuals with compromised immune systems, especially those with advanced HIV/AIDS" (Dao et al., 2024). "The fungus is found worldwide in the environment, particularly in soil and pigeon droppings, and is typically inhaled into the lungs, from which it can spread to the central nervous system, causing meningitis" (Dao et al., 2024; Siagian 2024; Bahn, et al., 2020).

"Cryptococcosis causes a high burden of disease worldwide with. mortality rates due to *C. neoformans* were 41%–61%" (Diniz-Lima et al., 2022). "The rising threat of *C. neoformans* is compounded by accumulating evidence for its ability to infect immunocompetent individuals and the emergence of antifungal-resistant variants" (Zhao et al., 2023). Complications happened in unexpected death of a 22-year-old man with cryptococcal meningoencephalitis which demonstrates, its fulminant course in previously well individuals (Tu & Byard, 2021), in the pediatric patient underwent renal transplant recipient (Gembillo et al., 2025), in persistently elevated intracranial pressure necessitating shunts (Jjunju et al., 2023), neurological worsening sequelae during treatment of an immunocompetent adult with *C. neoformans* meningitis (Tanu et al., 2020), immune reconstitution inflammatory syndrome (Shi et al., 2022) and even causing reversible deafness and blindness (Douglas-Vail et al., 2015). "The mortality rates were 10%–23% for central nervous system (CNS) and pulmonary infections, and ∼43% for bloodstream infections" (Dao et al., 2024). "Clinical studies in humans in combination with animal models of neurological cryptococcosis enabled the classification of the disease into different syndromes, including meningitis, encephalitis, meningoencephalitis, ventriculitis, increased intracranial pressure, and space-occupying lesions" (Rodrigues, 2016).

In the context of pharmacological management, the azole class of antifungals is commonly used, it works by inhibiting the enzyme 14-α-lanosterol demethylase (encoded by the ERG11 gene), which is essential for ergosterol production in the fungal cell membrane (Herrick et al., 2024). Unfortunately, there was alternately proof of reduced susceptibility of *C. neoformans* to fluconazole, itraconazole, ketoconazole and voriconazole (Melhem et al., 2024). Luckily, most *C. neoformans* isolates were still sensitive to Amphotericin B (Su et al., 2024).

"Cryptococcus exhibits several parasitic properties that enable it to infect and survive within a host, particularly in immunocompromised individuals by way of evading the host's immune cell surveillance" (Yang et al., 2022). It is considered an "accidental pathogen," as its virulence factors likely evolved for survival in the environment but can be co-opted for infection in mammals (Chen et al., 2022).

The main virulence factors of *C. neoformans* are its polysaccharide capsule (Casadevall et al., 2019) and the enzyme phenoloxidase, which produces melanin from exogenous tissue catecholamine precursors during infection (Baker et al., 2022). Other key factors include enzymes like urease (Toplis et al., 2020), phospholipase which is needed for its survival in the CNS (Hamed et al., 2023) and its extracellular peptidase that facilitate tissue invasion and fungal survival (Gutierrez-Gongora & Geddes-McAlister,2022). Its thermotolerance, which means its ability to grow at mammalian body temperature (37^0 C) (Ni et al., 2024) along with the ability to produce mannitol, occurs when glucose, fructose, or mannose are available as a carbon source, with high glucose concentrations inducing significant production, also facilitate its survival in their host (Guimarães et al., 2011). These combined factors help the fungus evade or escape the host's innate immune system (Denham & Brown, 2018; Yang, et al., 2017), invade tissues of vital organ (Chen et al., 2022), and survive inside the body of their host (Nielson et al., 2024). The following section will discuss about the polysaccharide capsule of *C. neoformans*.

2. POLYSACCHARIDE CAPSULE OF C. NEOFORMANS

The *Cryptococcus* capsule is a polysaccharide layer composed mainly of glucuronoxylomannan (GXM), glucuronoxylomannogalactan (GXMGal), and lesser mannoproteins. Its properties include being a key virulence factor that protects the fungus from the host's immune system by inhibiting phagocytosis and surviving inside macrophages. The capsule's composition is highly charged and can even modulate the host cell's internal environment.

Knowledge on the structures and physical properties, combined with Biochemical aspect of its composition, which mainly consist of GXM and GXMGal, and also the capsule itself is essential in understanding their role in cryptococcal pathogenesis and for the development of GXM-based therapeutic approaches.

2.1 Biochemical Properties

Capsular polysaccharides (CPSs) are an effective protective layer of high-molecular-weight carbohydrates on the surface of many microorganisms that function mostly as a virulence and also fitness factor (Zierke et al., 2025). Masquerading microbial pathogens basically facilitate by its capsular polysaccharides which mimic host-tissue molecules or have immunomodulatory effect on certain organ of the host (Hsieh & Allen, 2020; Cress et al., 2014). The critical Biochemical aspects of a polysaccharide capsule include (1) its biosynthesis via complex enzymatic pathways (Stephens, et al., 2023; Tien et al., 2022) and (2) its diverse Biochemical ingredients which can include various and specific monosaccharides and sugars (Laplanche et al., 2025; Singh, et al., 2019).

The diversity in composition is determined by the specific monosaccharides that make up the repeating units of the polymer (Imperiali, 2019), the way those units are linked (Fontana and Widmalm, 2023), and the presence of additional modifications contributes mainly to its role in virulence. The capsule is a protective layer of polysaccharides on the outer part of cell wall, essential for survival and virulence by evading the host immune system (Laplanche et al., 2025; Fontana & Widmalm, 2023; Imperiali, 2019; Singh, et al., 2019). Beside those already mention, its Biochemical properties, like negative its charge, are crucial for its function in resisting host defenses (Gao et al., 2024).

The polysaccharide capsule of *Cryptococcus* is primarily composed of polysaccharides such as glucuronoxylomannan (GXM) (Kuttel et al., 2020), galactoxylomannan (GalXM) (LaRocque-de-Freitas, et al., 2018), and mannoproteins (Teixeira et al., 2014) which described as follows:

- GXM is the main component (Kuttel et al., 2020), making up about 90% of the capsule's mass, and has an α-(1,3)-mannan backbone with attached β-(1,2)-glucuronic acid, xylosyl, and acetyl groups (Kadooka et al., 2024). This complex polymer is a key virulence factor that protects the fungus from the host's immune system, like the one reported just recently

by Enriquez et al that active *C.* neoformans glucuronoxylomannan production prevents elimination of cryptococcal CNS infection *in vivo* (Enriquez et al., 2025) and also has immunoregulatory effects (Guimarães-de-Oliveira et al., 2025). The structure of GXM varies between different serotypes, including in titanization and yeast form (Dos Santos et al., 2021; Probert, et al., 2019) and can be a target for therapies (da Silva et al. 2021).

- GalXM in the capsular polysaccharide of *Cryptococcus* (LaRocque-de-Freitas et al., 2018) is a smaller component with a more complex structure and is composed of α (1,6)-galactan which linked together α-(1→6) glycosidic bonds and trisaccharide motifs that can be substituted with glucuronyl residues (Vaishnav et al., 1998). These polysaccharides are released as exopolysaccharides (Grijpstra et al., 2009) which are very large macromolecules, and form a branched (Cordero et al., 2011), porous structure (Dorokhova et al., 2024) that is key to the fungus's virulence (De Jesus et al., 2010) by evading or even paralyzing the host immune system (Vecchiarelli et al., 2011; De Jesus et al., 2009).
- Mannoproteins are minor but important components of the *Cryptococcus* capsule (Teixeira et al., 2014). Despite their low percentage of the total capsule mass, mannoproteins are highly immunogenic (Levitz & Specht, 2006) and play roles in capsule structure, virulence, and immune response modulation just as revealed by Pietrella et al regarding the mannoproteins from *C. neoformans* promote Dendritic cell maturation and activation (Pietrella et al., 2005) or the T cell subset (Huang et al., 2002). For example, specific mannoproteins act as enzymes like chitin deacetylases to maintain cell wall integrity (Lee et al., 2023), while others type like Cmp1, are important for the overall capsule formation process (Han et al., 2020).

Even though said over and over again regarding the importance of main virulence factor of *C. neoformans,* namely the polysaccharide capsule; however, scholars must humbly hearted admit that, many fundamental aspects of capsule structure and function remain poorly understood. Better understanding of both, the Biochemical and physical properties of the *C. neoformans* polysaccharide capsule is critical because they are inextricably linked in determining the fungus's virulence and ability to evade the host immune system. The specific chemical composition dictates the capsule's overall physical characteristics, such as size, charge, and elasticity, which in turn directly affect its function in pathogenesis; and this become the next focus of discussion.

2.2 Physical Properties

Cryptococcus neoformans is actually surrounded by three concentric structures that separate the cell from the extracellular space: the plasma membrane, the cell walls and the polysaccharide (PS) capsule. The capsule physical composition is primarily composed of water (Maxson et al., 2007) which estimate reaching 99% of its total weight and therefore a highly hydrated structure with an index of refraction that is very close to that of aqueous medium (Cordero et al., 2013). Capsule regrowth experiments reveal dynamics of enlargement and architecture (Wear et al., 2022). This high water content makes the capsule appear transparent and undetectable under a routine light microscope examination (Nichols, 2021), as it has a similar refractive index to water and also due to its highly hydrophilic properties. To visualize it, a simple technique like India ink staining is used, which works by the water-filled capsule pushing the ink particles away (Suryowati, 2024; Siagian, 2024), creating a visible and discernable transparent halo around the cryptococcal cell (Nichols, 2021). The India ink particles formed a dark background that reveals the light-permeant capsule around yeast cells by contrast (Suryowati, 2024). India ink staining is simple, cheap, quick, and a commonly used standard for researchers who wish to visualize the capsule (Paes et al., 2018).

“The cryptococcal capsule contributed the most to the cell density such that cells with larger capsules had lower density than those with smaller capsules. Removing the capsule, by chemical or mechanical methods, increased the *C. neoformans* cell density and reduced buoyancy” (Vij et al., 2018). “The buoyancy of a microbial cell is an important physical characteristic that may affect its transportability in fluids and interactions with tissues during infection, especially in aqueous environment” (Jimenez et al., 2024).

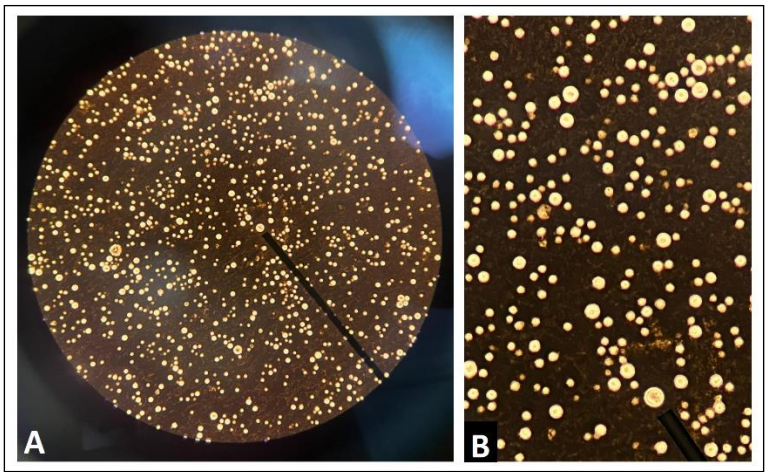

Fig. 1. *Cryptococcus neoformans* from niger seed agar culture stained with India Ink. (A) 400× magnification of routine light microscope, (B) optical magnification to show the size of capsule (specimen courtesy of the dept. of Parasitology, Faculty of Medicine, Universitas Kristen Indonesia, Jakarta-Indonesia

Regulation of *Cryptococcus* capsule size is arbitrated at the level of individual polysaccharide molecules or in other word in polymer level (Yoneda & Doering, 2008). Imaging studies reveal that the capsule architecture is consist of a meshwork of fibers which varies in density and also in porosity (Gates et al., 2004) with certain distance from the cell wall (Frases et al., 2009) and also related with certain growth conditions (Wear et al., 2022) and also coordinated with cell cycle progression (García-Rodas et al., 2014). The polysaccharide fibers are tightly packed and highly cross-linked in the inner layers, closer to the cell wall (Wang, et al., 2018). One of its physical characteristics is dense, less permeable region prevents larger host immune molecules, like antibodies and complement proteins, from reaching the fungal cell (Decote-Ricardo et al., 2019). At the outermost edge, the capsule becomes a more permeable, low-density meshwork (Vij et al., 2018). This peripheral region is more elastic (Araújo et al., 2021) and extends into the environment, where it can interact with host cells.

The thickness of the Cryptococcal capsule go beyond the measured length of individual GXM fibers (Yoneda & Doering, 2008). The *C. neoformans* capsule volume responds to environmental factors (Maxson et al., 2007), including iron levels and CO2 concentrations (Casadevall et al., 2019), which affect its mitochondrial activity (Trevijano-Contador et al., 2017). Although signaling pathways involved in capsule variation have been investigated, how the effect on physical changes happen is poorly understood.

“Factors that contribute to larger capsules are likely to be complex: they may include greater production and/or secretion of polysaccharides, more extensive polysaccharide assembly, decreased capsule shedding, and synthesis of structurally altered or larger polysaccharide molecules” (Crawford et al., 2020; O'Meara & Alspaugh, 2012; Frases, et al., 2009). According to Denham et al., “controlled secretion of Cryptococcal polysaccharide facilitate virulence and directly suppresses immune cell infiltration into the affected central nervous system” (Denham et al., 2018).

The average mass of *C. neoformans* GXM from four antigenically different strains ranged from 1.7 to 7 × 10^6 Daltons, as measured from Zimm plots of light-scattering data (McFadden et al., 2006). GalXM was significantly smaller than GXM, with an average mass of 1 × 10^5 Daltons (De Jesus et al., 2010, McFadden, et al., 2006). These data regarding molecular masses imply that GalXM is the most numerous polysaccharide content in the capsule on a molar basis, bearing a galactopyranose backbone with xylose and mannose side groups (LaRocque-de-Freitas et al., 2018). It also contains glucuronic acid that gives the negative charge to this polysaccharide (Chow & Casadevall, 2011).

Using technique measures the scattering of light by a molecule in a solution, which can be used to determine its size and shape, the radius of gyration of the capsular polysaccharides ranged between 68 and 208 nm, where this variability is likely due to strain-specific differences in the

length and structure of the polysaccharide molecules (Ding, et al., 2016; Cordero et al., 2011; McFadden, et al., 2006). According to Hargett, et al., the structure of a *C. neoformans* polysaccharide motif recognized by protective antibodies (Hargett et al., 2024). Neutron scattering analysis of *C. neoformans* polysaccharide uncovers solution rigidity and repeating fractal-like structural patterns (Wang et al., 2024). During infection, *C. neoformans* significantly changes their shape (remodeling) (Freitas et al., 2022) by upgrade and enlarges the dimension of the capsule through the addition of some new polysaccharide (Freitas et al., 2022; Trevijano-Contador, et al., 2017). Viscosity measurements suggest that neither polysaccharide altered fluid dynamics during infection (Freitas et al., 2022) since GXM behaved in solution as a polyelectrolyte, primarily due to the presence of negatively charged glucuronic acid side chains (Decote-Ricardo et al., 2019) and GalXM actually did not increase solution viscosity (Heiss et al., 2009). Immunoblot analysis also indicated heterogeneity within GXM. This significant heterogeneity in electrophoretic migration consistent with a heterogeneous composition (McFadden et al., 2005). In line with this, scanning transmission electron microscopy of GXM preparations disclosed a tangled network of two different types of molecules (Kuttel et al., 2020). Mass per length measurements from light scattering and scanning transmission electron microscopy were consistent to all portion and implied for GXM molecules self-aggregation which is dependent on divalent cations (Nimrichter et al., 2007). A mechanism for capsule growth is proposed based on the extracellular release and entanglement of GXM molecules (Wang et al., 2018; García-Rodas, et al., 2014). Lyophilization induces physicochemical alterations in cryptococcal exopolysaccharide by way of removing structural water molecules in the interior of the polysaccharide assemblies during extensive lyophilization (Wear et al., 2022).

External factors significantly affect the Biochemical and physical properties of the Cryptococcus capsular polysaccharide (CPS), influencing its size, composition, density, and immune-modulating properties. This dynamic change must be explored extensively, e.g., the effect of climate change in capsular size, virulence, geographic range and more, because it is a key virulence strategy that allows the fungus to survive and cause disease in a mammalian host by altering its capsule to evade the immune system.

3. CAPSULAR ELEMENT AS DIAGNOSTIC TOOLS

As a surprising findings, the capsule of the *Cryptococcus* fungus is a critical element in diagnosing cryptococcosis through both direct visualization and the detection of its major component, the capsular polysaccharide. The polysaccharide capsule is a unique feature of *C. neoformans* that distinguishes the organism from other medically important yeasts. Some primary diagnostic approaches leverage this feature: microscopy (Siagian, 2024; Suryowati, 2024) molecular (Diaz & Nguyen, 2011) and serological tests (Saha, et al., 2009). However, these methods and others have inherent limitations and variable reliability. A key challenge in staining *Cryptococcus* is always regarding visualizing its polysaccharide capsule, which is the organism's main virulence factor. The capsule is not visible with just routine stains because it is highly hydrophilic (Casadevall et al., 2019) and has a similar refractive index to the surrounding medium (Siagian, 2024). This has led to the development of specialized "negative staining" techniques, most notably the India ink stain, to make the capsule visible.

In the context of capsule screening, India ink is the common staining for direct screening of capsular element of *C. neoformans* (Siagian, 2024; Suryowati, 2024). Various histochemical stains react with cryptococci, including mucin stains such as mucicarmine which basically stain the gelatinous portion of capsule in this manner: aluminum in the Mucicarmine stain forms a chelating complex with carmine, which gives the complex a positive charge. This positive charge allows it to bind to the negatively charged, acidic substrates found in low-density mucin, leading to the stain being used to identify mucin and encapsulated fungi like *Cryptococcus* (Gurina & Simms, 2023; Misra, et al., 2023). Other stain such as alcian blue which according to Lee et al., is a successful method for identifying fungal spores and capsules (Lee et al., 2022), and periodic Acid-Schiff also aimed to stain the capsule by means of demonstrates the presence of certain polysaccharides, specifically glycogen and mucoproteins, which are present in the walls of the fungal hyphae. A positive periodic acid–Schiff stain is observed when the fungal hyphae appear bright red (Gurina & Simms, 2023; Mahoney et al., 2003) and Fontana-Masson

stain, which interacts with the cell wall where according to Bishop et al., especially for a positive result, it should be interpreted cautiously and only in the context of the organism's morphological features and host factors because many organisms in the morphological differential diagnosis of cryptococcosis can be Fontana-Masson silver stain positive (Bishop et al., 2012).

However, these approach of staining have fundamental limitations and variable reliability, and even in the most ideal research settings, the unique properties of the cryptococcal capsule itself present difficulties in making visualization possible. Several challenges in staining *Cryptococcus* still present opportunities for improvement, particularly concerning the low sensitivity of older methods like India ink, the visualization of capsule-deficient strains, and specimen quality issues. While newer diagnostic methods might exist, improvements to microscopy techniques and clinical sample preparation and handling could still always be beneficial, especially in resource-limited settings.

4. CONCLUSION

Cryptococcus neoformans is a major opportunistic pathogen which is recently considered as reemerging fungal disease. Cryptococcosis has become much more prominent globally due to the increase in immunosuppressed and immunocompromised populations. The fungus has a worldwide distribution and varied clinical presentations, causing high morbidity and mortality among human populations.This fungus is a pure facultative intracellular fungal pathogen and presents itself as a pathogen with a virulence capacity known as "ready virulence." Its capsule is essential for its ability to cause lethal cryptococcosis, particularly in immunocompromised patients. In *C. neoformans*, the components of the capsular network constitute the main fungal virulence factor as well as a precious element for simple detection for rapid screening on fresh clinical sample such as LCS, even though challenge and gaps are still existing, but room for improvement is still always available.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that no generative ai technologies such as large language models (chatgpt, copilot, etc.) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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