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VMP1 in *Plasmodium*: Molecular Functions, Roles in Parasite Survival, and Therapeutic Perspectives

[1]Suhasini. G*., [2]Surender Reddy. K and [3]Madhulekha R.
[1]Department of Zoology, Pingle Govt College for Women (A), Hanumakonda
[2]Department of Zoology, Govt College, SRR Govt Arts & Science College, Karimnagar
[3]Gandhi Institute of Medical Sciences and Research, Visakhapatnam
*Corresponding Author: *zoopingle24@gmail.com*

Abstract

Background: Malaria remains a major global health challenge, primarily caused by *Plasmodium* species, particularly *Plasmodium falciparum*. The increasing emergence of antimalarial drug resistance highlights the need to identify novel parasite-specific molecular targets. Vesicle-associated membrane protein 1 (**VMP1**) has emerged as an important cellular protein associated with membrane dynamics, autophagy, intracellular trafficking, and parasite survival. However, its biological significance in *Plasmodium* and related apicomplexan parasites remains insufficiently explored.

Objective: This review summarises and critically evaluates current knowledge of VMP1 in *Plasmodium*, with particular emphasis on its molecular functions, involvement in parasite development and survival, cellular trafficking, and potential as a therapeutic target.

Key Areas Reviewed: The review first discusses the structural and functional characteristics of VMP1 and its conserved roles in eukaryotic membrane-associated processes. It then examines the possible contribution of VMP1 to intracellular vesicle formation, organelle homeostasis, protein trafficking, autophagy-related pathways, and cellular organization in malaria parasites. Evidence from *Plasmodium* and closely related apicomplexan parasites, including *Toxoplasma gondii*, is considered to understand the evolutionary and functional significance of VMP1. Particular attention is given to experimental evidence indicating that disruption or depletion of VMP1 can impair parasite development, cellular organization, and pathogenicity.

Therapeutic Significance: The review further explores VMP1 as a potential molecular target for antimalarial drug development. Targeting essential VMP1-associated pathways may interfere with parasite survival while providing opportunities for developing novel therapeutic strategies against drug-resistant malaria. Potential approaches for VMP1-targeted intervention, including small-molecule inhibitors and pathway-specific strategies, are also discussed.

Future Perspectives: Finally, the review identifies major research gaps, including the need for detailed structural characterization of VMP1, elucidation of its interacting proteins and molecular pathways, validation of parasite-specific functions, and evaluation of VMP1-targeted compounds in appropriate experimental models. Understanding these mechanisms could facilitate the development of innovative interventions against malaria and other apicomplexan parasitic diseases.

Keywords: VMP1; *Plasmodium*; *Plasmodium falciparum*; malaria; parasite survival; membrane trafficking; autophagy; apicomplexan parasites; therapeutic target; antimalarial drug development.

1. Introduction

Malaria remains one of the most important parasitic diseases worldwide and continues to pose a major challenge to global public health. The disease is caused by intracellular protozoan parasites of the genus *Plasmodium* and is transmitted predominantly through the bites of infected female *Anopheles* mosquitoes. According to the World Health Organisation (WHO), an estimated 282 million malaria cases and 610,000 malaria-related deaths occurred in 2024 across 80 countries. The WHO African Region continues to bear the greatest burden, accounting for approximately 95% of global malaria cases and deaths. Children under five years of age remain particularly vulnerable to severe malaria and death (World Health Organization, 2025a; World Health Organization, 2025b).Despite considerable progress in malaria prevention, diagnosis, vaccination, and treatment, the disease continues to impose a substantial health, social, and economic burden, particularly in resource-limited settings. Recurrent infections, severe disease, loss of productivity, school absenteeism, healthcare expenditure, and reduced economic development contribute to the continuing impact of malaria (World Health Organisation, 2025b).

Plasmodium Species Causing Human Malaria

Human malaria is primarily caused by five *Plasmodium* species: ***Plasmodium falciparum, P. vivax, P. malariae, P. ovale*** and the zoonotic ***P. knowlesi***. Among these species, *P. falciparum* and *P. vivax* account for the majority of the global malaria burden. *P. falciparum* is particularly important because it is responsible for most severe malaria cases and malaria-related deaths, especially in sub-Saharan Africa (World Health Organisation, 2025a; Centres for Disease Control and Prevention, 2024).

P. vivax has the widest geographical distribution outside sub-Saharan Africa and is characterized by its ability to form dormant liver-stage hypnozoites, which can reactivate and cause recurrent infections. *P. malariae* generally produces prolonged blood-stage infections, whereas *P. ovale* can also establish dormant liver stages. *P. knowlesi*, a zoonotic parasite naturally maintained in macaques in Southeast Asia, can infect humans and cause severe disease because of its rapid erythrocytic replication cycle (Centres for Disease Control and Prevention, 2024).

Increasing Antimalarial Drug Resistance

The emergence and spread of **antimalarial drug resistance** represents a major threat to sustainable malaria control. *P. falciparum* has developed resistance to several historically important antimalarial drugs, including chloroquine and sulfadoxine–pyrimethamine. More recently, partial resistance to artemisinin derivatives has emerged in several regions, threatening the effectiveness of artemisinin-based combination therapies (ACTs), which remain central to malaria treatment (World Health Organization, 2025b; Centers for Disease Control and Prevention, 2024).

Drug resistance can develop through genetic changes that reduce parasite susceptibility to antimalarial compounds. Inappropriate treatment, inadequate drug exposure, poor-quality medicines, and incomplete adherence can facilitate the selection and spread of resistant parasites. Molecular surveillance and genomic

approaches are increasingly being used to identify resistance-associated mutations and monitor their geographical distribution (Ashley et al., 2014; Uwimana et al., 2020).

The continuing evolution of drug resistance emphasizes the urgent need to identify new parasite-specific molecular targets. Ideally, such targets should be essential for parasite survival or development, sufficiently distinct from host proteins to permit selective inhibition, and suitable for pharmacological intervention.

Need for Novel Molecular Targets

The identification of new antimalarial targets increasingly focuses on essential parasite processes, including protein trafficking, lipid metabolism, membrane homeostasis, organelle biogenesis, and intracellular signalling. Advances in genomics, transcriptomics, proteomics, chemical genetics, CRISPR-based functional genomics, and high-throughput screening have substantially expanded the ability to identify parasite vulnerabilities (Cowell and Winzeler, 2019; Zhang et al., 2018).

Membrane-associated proteins are particularly attractive targets because *Plasmodium* parasites possess highly specialized membrane systems and organelles that are essential for intracellular growth, host-cell invasion, replication, nutrient acquisition, and egress. Consequently, proteins involved in membrane organization, lipid transport, and organelle biogenesis may provide opportunities for developing novel antimalarial interventions.

VMP1: An Emerging Molecular Target

Vacuole membrane protein 1 (VMP1) is a multi-pass membrane protein belonging to the **DedA superfamily**. In eukaryotic systems, VMP1 has been associated with endoplasmic reticulum (ER) organisation, membrane homeostasis, lipid metabolism, autophagy, and ER–organelle communication (Molejon et al., 2013; Zhao et al., 2017).

Recent research has provided important new insights into VMP1 biology in apicomplexan parasites. **Reddy et al. (2025)** identified VMP1 in both ***P. falciparum*** and ***Toxoplasma gondii*** and demonstrated that these proteins function as **ER-localized lipid scramblases**. This finding provides direct evidence linking VMP1 to lipid mobilisation, ER organisation, lipid-droplet homeostasis, and secretory-organelle biogenesis in apicomplexan parasites.

Molecular and Cellular Functions of VMP1

VMP1 has several important cellular functions:

- **Membrane homeostasis:** VMP1 contributes to the organisation and maintenance of cellular membranes.
- **Lipid transport and distribution:** VMP1 facilitates lipid redistribution between membrane leaflets.
- **Endoplasmic reticulum function:** VMP1 contributes to ER organisation and ER–organelle contact sites.
- **Autophagy:** VMP1 is associated with autophagosome formation and autophagy-related membrane dynamics.
- **Lipid-droplet homeostasis:** VMP1 contributes to lipid-droplet formation and lipid distribution.
- **Organelle communication:** VMP1 participates in dynamic interactions between the ER and other intracellular compartments (Calì et al., 2008; Molejon et al., 2013; Zhao et al., 2017).

These functions are particularly relevant to apicomplexan parasites because their growth and survival require extensive membrane remodelling and coordinated formation of specialised secretory organelles.

VMP1 in *Plasmodium* and *Toxoplasma*

Recent experimental evidence has established that **PfVMP1 and TgVMP1 are localised to the ER and possess lipid-scrambling activity** (Reddy et al., 2025). Depletion of TgVMP1 in *T. gondii*

resulted in major defects in parasite development, motility, host-cell invasion, and egress.

VMP1 depletion was also associated with impaired **rhoptry and dense-granule biogenesis**, reduced microneme and rhoptry secretion, altered ER organisation, and disruption of lipid-droplet homeostasis (Reddy et al., 2025). Because micronemes, rhoptries, and dense granules are essential for parasite motility, host-cell invasion, intracellular development, and egress, these observations provide an important mechanistic connection between VMP1-dependent lipid homeostasis and parasite fitness.

Importantly, functional complementation experiments demonstrated that PfVMP1 could rescue defects associated with TgVMP1 depletion, supporting functional conservation of VMP1-dependent lipid-scrambling activity among apicomplexan parasites (Reddy et al., 2025).

Potential Role of VMP1 in Parasite Survival

The available evidence supports a model in which VMP1 contributes to parasite fitness through the maintenance of ER lipid homeostasis and membrane organisation:

VMP1 → ER lipid homeostasis → membrane organization → secretory-organelle biogenesis → parasite development and invasion → parasite survival

The strongest experimental evidence for this pathway currently comes from *T. gondii*, whereas the precise stage-specific functions of PfVMP1 in *P. falciparum* require further investigation. Therefore, findings from *T. gondii* should be used as comparative evidence rather than automatically interpreted as direct evidence for identical functions in *P. falciparum* (Reddy et al., 2025).

Therapeutic Significance of VMP1

The essential role of membrane and secretory pathways in apicomplexan parasites makes VMP1 an intriguing candidate for future therapeutic investigation. Pharmacological disruption of VMP1-dependent lipid homeostasis could potentially interfere with ER function, membrane organization, secretory-organelle biogenesis, and parasite development (Reddy et al., 2025).

However, VMP1 should currently be regarded as an **emerging potential target rather than a clinically validated antimalarial target**. Important questions remain regarding the precise structure of PfVMP1, its essentiality at different parasite life-cycle stages, its interacting proteins, and the feasibility of selectively inhibiting parasite VMP1 without affecting host VMP1.

Research Gaps and Future Perspectives

Future research should combine **CRISPR/Cas-based genetics, conditional protein depletion, proteomics, lipidomics, structural biology, molecular modelling, and chemical screening** to define the precise biological functions of PfVMP1.

Particular attention should be given to determining whether PfVMP1 is essential during different stages of the *Plasmodium* life cycle, including asexual blood stages, gametocytes, mosquito stages, and liver stages. Identification of parasite-specific structural features may facilitate the development of selective VMP1 inhibitors.

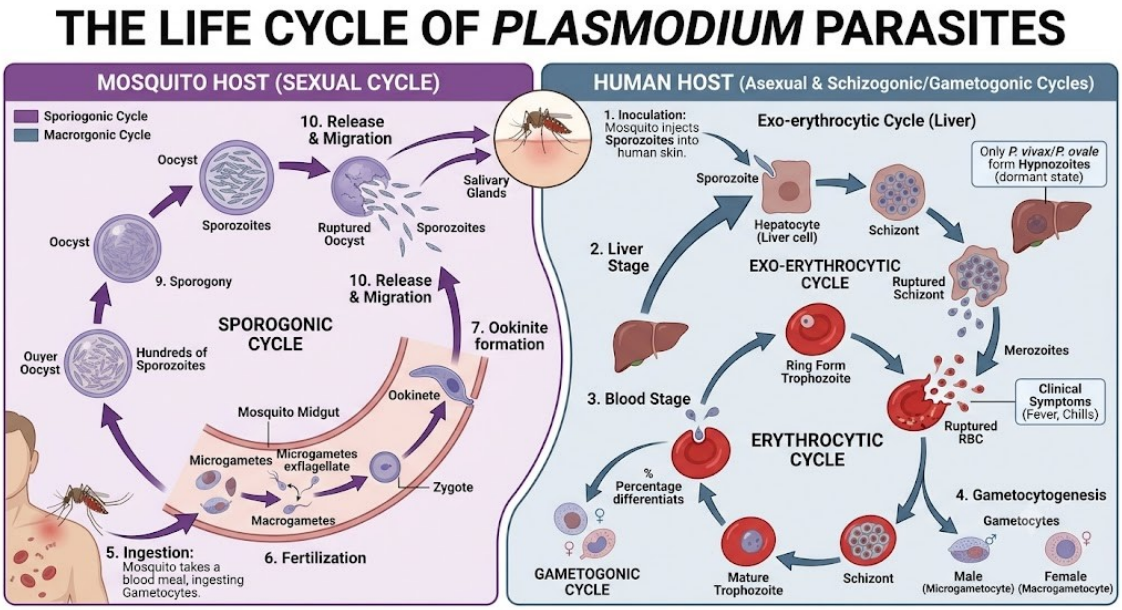
Comparative studies of VMP1 in *P. falciparum*, *T. gondii*, and other apicomplexans may also reveal conserved mechanisms and parasite-specific vulnerabilities. The recent demonstration of VMP1-dependent lipid scrambling provides a strong foundation for these investigations (Reddy et al., 2025).

2. Overview of *Plasmodium* Biology

2.*Plasmodium* Life Cycle and Parasite Development

The life cycle of *Plasmodium* is complex and alternates between **human and female *Anopheles* mosquito hosts**. It comprises asexual multiplication in humans and sexual reproduction

in the mosquito. Understanding these developmental stages is essential for evaluating proteins such as VMP1 that may regulate parasite growth, membrane organization, organelle biogenesis, and survival.



2.1 Mosquito-to-Human Transmission

During the bite of an infected female *Anopheles* mosquito, **sporozoites** are injected into the human bloodstream with mosquito saliva. The sporozoites rapidly migrate to the liver and invade hepatocytes (Cowman et al., 2016; World Health Organization, 2025).

2.2 Liver Stage

Within hepatocytes, sporozoites undergo **exo-erythrocytic development**, transforming into schizonts through repeated nuclear division. Mature schizonts release thousands of **merozoites**into the bloodstream. In *P. vivax* and *P. ovale*, a proportion of parasites can remain dormant as **hypnozoites**, which may reactivate months or even years later and cause relapse (Ménard et al., 2013; White, 2011).

2.3 Blood Stage

The released merozoites invade **red blood cells (erythrocytes)** and sequentially develop through the **ring, trophozoite, and schizont stages**. Mature schizonts undergo egress, releasing new merozoites that invade additional erythrocytes and repeat the cycle. This erythrocytic stage is responsible for the major clinical manifestations of malaria, including fever, chills, anemia, and, in severe cases, organ dysfunction (Cowman et al., 2016; Milner, 2018).

2.4 Gametocyte Formation

A proportion of blood-stage parasites differentiate into sexual forms known as **male and female gametocytes** rather than continuing asexual replication. Mature gametocytes circulate in the peripheral blood and are taken up by feeding female *Anopheles* mosquitoes, thereby enabling transmission from humans to mosquitoes (Baker, 2010; Josling and Llinás, 2015).

2.5 Sexual Development in the Mosquito

Following ingestion by a mosquito, gametocytes differentiate into male and female gametes in the mosquito midgut. Fertilization produces a **zygote**,

which develops into a motile **ookinete**. The ookinete penetrates the mosquito midgut wall and develops into an **oocyst**. Through **sporogony**, the oocyst produces numerous sporozoites. These migrate to the mosquito salivary glands and become capable of infecting another human host during a subsequent blood meal (Aly et al., 2009; Cowman et al., 2016).

2.6 Biological Significance of the *Plasmodium* Life Cycle

The *Plasmodium* life cycle involves extensive changes in **cellular architecture, membrane dynamics, lipid metabolism, protein trafficking, and specialized organelle biogenesis**. These processes are particularly important during host-cell invasion, intracellular replication, parasite egress, and transmission. Specialized organelles such as **micronemes, rhoptries, and dense granules** play essential roles in parasite invasion and development, particularly in apicomplexan parasites (Bannister and Mitchell, 2003; Cowman et al., 2017).

Understanding these stage-specific cellular processes provides an important framework for investigating **VMP1**, particularly its potential involvement in ER membrane organisation, lipid homeostasis, and secretory-organelle biogenesis in *Plasmodium* (Reddy et al., 2025).

3. VMP1: Structure, Conservation and Molecular Characteristics

Vacuole membrane protein 1 (VMP1) is a highly conserved, multi-pass transmembrane protein belonging to the **DedA protein superfamily**. In mammals, the *VMP1* gene encodes an endoplasmic-reticulum (ER)-localized membrane protein containing multiple transmembrane helices. VMP1 is involved in membrane homeostasis, lipid metabolism, organelle communication, and autophagy-related processes (Calì et al., 2008; Molejon et al., 2013; Zhao et al., 2017).

In apicomplexan parasites, including *Plasmodium falciparum* and *Toxoplasma gondii*, VMP1 is also associated with the ER. Recent evidence indicates that parasite VMP1 functions as a **lipid scramblase**, facilitating the redistribution of lipids across ER membrane leaflets and contributing to membrane and organelle homeostasis (Reddy et al., 2025).

3.2 Subcellular Localisation

VMP1 is predominantly localised to the **endoplasmic reticulum**, where it participates in membrane organisation and lipid homeostasis. ER localisation is particularly important because the ER serves as a major site of lipid synthesis, protein processing, membrane biogenesis, and intracellular trafficking.

In *T. gondii*, TgVMP1 has been experimentally localised to the ER, while recent studies have demonstrated similar ER localisation of PfVMP1 in *P. falciparum* (Reddy et al., 2025). This conserved localisation suggests that VMP1 may perform fundamental membrane-associated functions across apicomplexan parasites.

3.3 Conserved Structural Features

VMP1 is characterised by multiple **transmembrane α-helices** that enable it to function as an integral membrane protein. It belongs to the DedA superfamily, a diverse group of membrane proteins involved in cellular ion and lipid homeostasis.

A particularly important functional characteristic of VMP1 is its ability to act as a **phospholipid scramblase**. Rather than transporting lipids through a classical ATP-dependent mechanism, lipid scramblases facilitate the movement of phospholipids between the two leaflets of a membrane. This activity is important for maintaining membrane lipid asymmetry and supporting membrane remodelling (Reddy et al., 2025).

3.4 VMP1 Across Eukaryotes

VMP1-related proteins occur across diverse eukaryotic organisms, indicating an ancient evolutionary origin. In mammalian cells, VMP1 has been studied extensively in relation to

autophagy, ER homeostasis, lipid metabolism, and ER–organelle contact sites (Molejon et al., 2013; Zhao et al., 2017).

The conserved presence of VMP1-like proteins in different eukaryotic lineages suggests that its fundamental role is associated with maintaining membrane and lipid homeostasis. However, the precise biological functions of VMP1 can differ according to cellular context and organismal complexity.

3.5 Conservation in *Plasmodium* and Apicomplexans

VMP1 is conserved in several apicomplexan parasites, including ***P. falciparum*** **and** ***T. gondii***. This conservation is particularly significant because apicomplexans possess complex intracellular membrane systems and specialised secretory organelles that are essential for invasion, intracellular development, and egress.

Reddy et al. (2025) demonstrated that PfVMP1 and TgVMP1 share important functional properties, including ER localisation and lipid-scrambling activity. Furthermore, functional complementation experiments indicated that PfVMP1 can compensate for the loss of TgVMP1 function, supporting **functional conservation between malaria parasites and other apicomplexans**.

This observation suggests that VMP1-dependent lipid homeostasis may represent an evolutionarily conserved cellular mechanism within Apicomplexa.

3.6 VMP1-Interacting Proteins and Molecular Partners

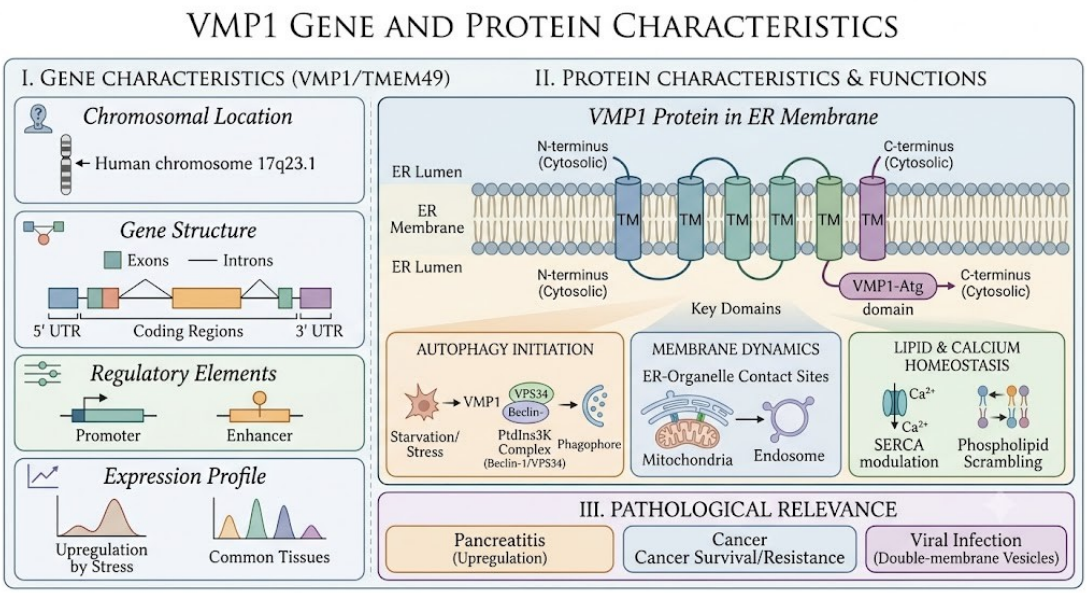
In non-parasitic eukaryotic systems, VMP1 interacts with proteins involved in **autophagy, ER organisation, lipid metabolism, and membrane-contact-site regulation**. These interactions help coordinate membrane remodelling and intracellular organelle communication.

In mammalian cells, VMP1 has been associated with components of the autophagy machinery, including **Beclin-1**, and with proteins involved in ER–organelle contact sites and lipid homeostasis (Molejon et al., 2013; Zhao et al., 2017).

In apicomplexan parasites, the complete VMP1 interactome remains insufficiently characterised. Identification of PfVMP1-interacting proteins represents an important area for future research because these molecular partners may reveal the pathways through which VMP1 regulates ER lipid homeostasis, secretory-organelle biogenesis, parasite invasion, and survival (Reddy et al., 2025). (Table-1)

Table-1 Summary of VMP1 Characteristics

Feature	Current understanding
Protein	Vacuole membrane protein 1 (VMP1)
Protein family	DedA superfamily
Localization	Predominantly endoplasmic reticulum
Topology	Multi-pass transmembrane protein
Major function	Lipid scrambling and membrane homeostasis
Other functions	ER organisation, lipid metabolism, autophagy-related processes
Apicomplexan conservation	Present in *P. falciparum*, *T. gondii* and related parasites
Parasite significance	Linked to lipid homeostasis and secretory-organelle biogenesis
Therapeutic relevance	Potential emerging target for antiparasitic drug development
Major knowledge gap	Detailed PfVMP1 structure, interactome and stage-specific functions



4. Molecular Functions of VMP1

Vacuole membrane protein 1 (**VMP1**) is an evolutionarily conserved integral membrane protein that participates in several aspects of cellular membrane and lipid homeostasis. Although VMP1 has been extensively investigated in mammalian and other eukaryotic systems, its functions in apicomplexan parasites are only beginning to be elucidated. Therefore, it is important to distinguish **well-established functions demonstrated in non-parasitic eukaryotes** from **experimentally supported and proposed functions in *Plasmodium* and related apicomplexans**.

4.1 Membrane Organization and Lipid Homeostasis

One of the best-established functions of VMP1 is its involvement in **membrane organization and lipid homeostasis**. VMP1 is an integral membrane protein of the endoplasmic reticulum (ER) and contributes to the maintenance of appropriate membrane lipid composition and distribution. Recent structural and functional studies have identified VMP1/TMEM41B-family proteins as membrane lipid scramblases that facilitate the redistribution of phospholipids between the two leaflets of biological membranes (Ghanbarpour et al., 2021; Reddy et al., 2025).

In apicomplexan parasites, this function appears particularly important because extensive membrane remodeling accompanies parasite growth, replication, invasion, and egress. Reddy et al. (2025) demonstrated that VMP1 functions as an **ER-resident lipid scramblase in *P. falciparum* and *T. gondii***. Thus, lipid redistribution represents one of the strongest experimentally supported functions of VMP1 in apicomplexans.

Evidence level: Well established for membrane/lipid homeostasis; **experimentally demonstrated in apicomplexans**.

4.2 Vesicle Formation and Membrane Trafficking

VMP1 is also associated with membrane remodeling and the formation of membrane structures involved in intracellular trafficking. By influencing lipid distribution and membrane curvature, VMP1 can affect the formation and maturation of specialized membrane compartments.

In mammalian systems, VMP1 has been linked to ER membrane remodeling and autophagic membrane formation (Molejon et al., 2013; Zhao et al., 2017). In apicomplexan parasites, recent evidence suggests that VMP1-dependent lipid homeostasis is required for the proper formation and function of specialized secretory organelles.

In *T. gondii*, depletion of VMP1 resulted in defects in **rhoptry and dense-granule biogenesis** and impaired secretion from micronemes and rhoptries (Reddy et al., 2025). Because these organelles are essential for parasite invasion and egress, VMP1-mediated membrane organization may indirectly regulate parasite trafficking and secretion.

Evidence level: Well supported for membrane remodeling in eukaryotes; experimentally supported for secretory-organelle biogenesis in *T. gondii*; mechanisms in *P. falciparum* remain under investigation.

4.3 Endoplasmic-Reticulum-Associated Processes

The **endoplasmic reticulum is the principal cellular location of VMP1**. Consequently, many of its functions are closely associated with ER organization, lipid metabolism, membrane contact sites, and cellular stress responses.

The ER is responsible for lipid synthesis, protein folding, membrane production, and communication with mitochondria, lipid droplets, and other organelles. VMP1 contributes to maintaining ER membrane properties and lipid balance. Disruption of VMP1 can therefore disturb ER homeostasis and alter downstream cellular processes.

In apicomplexans, Reddy et al. (2025) demonstrated that VMP1 is localized to the ER and contributes to lipid homeostasis. Alteration of VMP1 function in *T. gondii* resulted in abnormalities in ER organization and lipid-droplet homeostasis, indicating an important connection between VMP1 and parasite ER physiology.

Evidence level:Well established in eukaryotic cells and experimentally demonstrated in apicomplexans.

4.4 Autophagy and Cellular Recycling

VMP1 was initially recognized as an important regulator of **autophagy**, the cellular process responsible for degrading and recycling damaged proteins and organelles. VMP1 can participate in the initiation of autophagic membrane formation and interact with components of the autophagy machinery (Molejon et al., 2013).

Through autophagy, cells maintain homeostasis during nutrient limitation, cellular stress, and organelle damage. VMP1-dependent membrane remodeling contributes to the formation of autophagic structures and their progression through the autophagy pathway.

However, caution is required when extrapolating this function to *Plasmodium*. Although autophagy-related pathways are present in malaria parasites, **the precise contribution of PfVMP1 to canonical autophagy and parasite-specific recycling pathways has not yet been fully established**.

Evidence level:Well established in several eukaryotic systems; parasite-specific role remains largely proposed and requires further experimental validation.

4.5 Organelle Homeostasis

VMP1 contributes to **organelle homeostasis** by maintaining appropriate lipid composition, membrane structure, and communication between intracellular compartments. The ER is closely connected with mitochondria, lipid droplets, lysosomes, and other membrane-bound organelles, and disruption of VMP1 can affect these interactions.

In apicomplexan parasites, organelle homeostasis is particularly important because they contain highly specialized structures such as **micronemes, rhoptries, dense granules, apicoplasts, and mitochondria**. Recent work has shown that VMP1 depletion in *T. gondii* affects the biogenesis and function of secretory organelles, providing experimental evidence that VMP1 contributes to parasite organelle homeostasis (Reddy et al., 2025).

For *P. falciparum*, the role of VMP1 in maintaining specific organelles requires further investigation.

Evidence level:Well supported generally; experimentally demonstrated for secretory-organelle biology in *T. gondii*; partly proposed for *P. falciparum*.

4.6 Protein Transport and Secretory Pathways

The ER is the starting point for the synthesis and trafficking of many secretory and membrane proteins. By maintaining ER membrane architecture and lipid composition, VMP1 may indirectly influence protein trafficking through the secretory pathway.

Evidence from apicomplexans suggests that VMP1 dysfunction can affect **protein secretion from specialized parasite organelles**. In *T. gondii*, VMP1 depletion impaired microneme and rhoptry secretion, which are essential for host-cell invasion and parasite egress (Reddy et al., 2025).

However, it is important to distinguish **direct protein transport activity** from an indirect effect caused by altered membrane lipid composition. At present, VMP1 is better characterized as a regulator of membrane and lipid homeostasis rather than as a conventional protein transporter.

Evidence level: Indirectly supported; strong evidence for effects on secretory-organelle function in *T. gondii*, but direct protein-transport activity has not been established**.**

4.7. Maintenance of Cellular Integrity

By regulating membrane lipids, ER organisation, organelle communication, and intracellular membrane dynamics, VMP1 contributes to **overall cellular integrity and survival**.

Loss or depletion of VMP1 can disrupt membrane homeostasis and produce downstream defects in organelle function and cellular viability. In *T. gondii*, VMP1 depletion causes profound defects in parasite development, motility, invasion, and egress, demonstrating the importance of VMP1-dependent cellular homeostasis for parasite fitness (Reddy et al., 2025).

In *P. falciparum*, however, the precise contribution of PfVMP1 to parasite viability, developmental progression, and pathogenicity remains an important area for future investigation.

Evidence level: Well supported in eukaryotic systems; experimentally demonstrated for parasite fitness in *T. gondii*; requires further validation in *P. falciparum*.

Table 2: Evidence-Based Classification of VMP1 Functions

VMP1 function	Evidence in eukaryotes	Evidence in apicomplexans	Status in *P. falciparum*
Membrane organization	Strong	Strong	Supported
Lipid homeostasis/scrambling	Strong	Strong	Experimentally demonstrated
ER organization	Strong	Strong	Supported
Vesicle/membrane remodelling	Strong	Moderate–strong	Under investigation
Secretory-organelle biogenesis	Moderate	Strong in *T. gondii*	Requires further study
Autophagy	Strong	Limited	Not fully established
Organelle homeostasis	Strong	Strong in *T. gondii*	Partly characterized
Protein transport	Indirect	Indirect/strong effect on secretion	Not established as direct function
Cellular integrity/survival	Strong	Strong in *T. gondii*	Requires further validation

4.8 Maintenance of Cellular Integrity

By regulating membrane lipids, ER organisation, organelle communication, and intracellular membrane dynamics, VMP1 contributes to **overall cellular integrity and survival**.

Loss or depletion of VMP1 can disrupt membrane homeostasis and produce downstream defects in organelle function and cellular viability. In *T. gondii*, VMP1 depletion causes profound defects in parasite development, motility, invasion, and egress, demonstrating the importance of VMP1-dependent cellular homeostasis for parasite fitness (Reddy et al., 2025).

In *P. falciparum*, however, the precise contribution of PfVMP1 to parasite viability, developmental progression, and pathogenicity remains an important area for future investigation. Evidence level: Well, supported in eukaryotic systems; experimentally demonstrated for parasite fitness in *T. gondii*; requires further validation in *P. falciparum*.

4.9 Established versus Proposed Functions

It is important to maintain a clear distinction between **established**, **experimentally supported**, and **proposed** functions of VMP1. Its roles in **ER localization, membrane organization, lipid homeostasis, and lipid scrambling** are strongly supported by experimental evidence. In apicomplexan parasites, recent work has demonstrated VMP1-dependent effects on **secretory-organelle biogenesis, lipid-droplet homeostasis, invasion, motility, and egress**, particularly in *T. gondii* (Reddy et al., 2025).

In contrast, the specific roles of PfVMP1 in **canonical autophagy, direct protein transport, and all stages of the *P. falciparum* life cycle** remain incompletely defined. These functions should therefore be presented as **potential or proposed mechanisms** rather than established facts. This distinction is particularly important for a review article because it prevents extrapolation from mammalian systems or *T. gondii* to *P. falciparum* without sufficient experimental evidence

5. VMP1 in *Plasmodium* and Related Apicomplexan Parasites

Vacuole membrane protein 1 (VMP1) has recently emerged as a potentially important regulator of membrane and lipid homeostasis in apicomplexan parasites. Although VMP1 biology has been extensively investigated in mammalian and other eukaryotic systems, direct experimental information in malaria parasites remains limited. A major advance was provided by Reddy et al. (2025), who identified and characterised VMP1 homologues in Plasmodium falciparum and Toxoplasma gondii and demonstrated that both proteins function as endoplasmic-reticulum (ER)-localised lipid scramblases.

5.1 VMP1 in Plasmodium falciparum

The *P. falciparum* genome contains a VMP1 homologue designated PfVMP1 (PF3D7_1474600). Bioinformatic analysis showed that PfVMP1 contains the characteristic multi-pass transmembrane architecture and DedA domain of the VMP1/DedA superfamily. The protein also contains conserved sequence motifs and predicted re-entrant loops characteristic of this protein family. Structural modelling further indicated substantial similarity between PfVMP1 and human VMP1, supporting its classification as a functional VMP1 homologue (Reddy et al., 2025).

Importantly, experimental studies demonstrated that PfVMP1 is localised to the ER and possesses lipid-scrambling activity. This observation is significant because the ER is a major site of lipid synthesis, membrane biogenesis, and intracellular membrane trafficking. Thus, PfVMP1 may contribute to maintaining the lipid composition required for parasite membrane formation and organelle development (Reddy et al., 2025).

However, the available evidence should be interpreted carefully. While PfVMP1 has been characterised biochemically and structurally, the complete stage-specific biological role of PfVMP1 in the *P. falciparum* life cycle has not yet been established. In particular, further studies are required to determine whether PfVMP1 is essential during asexual blood-stage replication, gametocytogenesis, mosquito development, or liver-stage development.

5.2 VMP1 in Other Plasmodium Species

Compared with P. falciparum, experimental information on VMP1 in other Plasmodium species remains very limited. Nevertheless, comparative genomic analysis indicates that VMP1 homologues occur among several apicomplexan parasites, with substantial sequence conservation between homologues. The conservation of the characteristic DedA domain and transmembrane organisation suggests that VMP1-related proteins may perform broadly conserved membrane-associated functions (Reddy et al., 2025).

This conservation provides a useful basis for investigating VMP1 in other malaria parasites, including *P. vivax*. However, the presence of a homolog alone does not establish identical biological function. Experimental validation involving gene disruption or conditional depletion, localisation studies, lipidomics, and functional complementation will be required to determine whether VMP1 performs equivalent functions across different Plasmodium species.

5.3 VMP1 in *Toxoplasma gondii*

The strongest functional evidence for parasite VMP1 currently comes from *Toxoplasma gondii.* TgVMP1 is an ER-localized multi-pass membrane protein with a conserved DedA domain and lipid-scrambling activity. Conditional depletion of TgVMP1 produced substantial defects in parasite biology, including impaired intracellular development, motility, host-cell invasion, and egress (Reddy et al., 2025).

TgVMP1 depletion also caused defects in the formation and function of specialised secretory organelles. In particular, rhoptry and dense-granule biogenesis was impaired, while secretion from micronemes and rhoptries was reduced.

These organelles are essential for parasite motility, host-cell invasion, establishment of the intracellular parasitophorous vacuole, and egress. Therefore, the findings provide a mechanistic link between VMP1-dependent ER lipid homeostasis and parasite developmental fitness.

TgVMP1 depletion additionally disturbed ER organisation and lipid-droplet homeostasis, demonstrating that VMP1 activity extends beyond a single organelle and contributes to broader cellular membrane homeostasis. Loss of the intravacuolar network was also observed, further demonstrating the importance of VMP1-dependent cellular organisation for T. gondii development (Reddy et al., 2025).

5.4 Functional Conservation Between *P. falciparum* and *T. gondii*

One of the most important observations for malaria research is the functional complementation of TgVMP1-deficient parasites by PfVMP1. Reddy et al. (2025) showed that expression of PfVMP1 could rescue defects caused by TgVMP1 depletion. Remarkably, human VMP1 was also capable of functional complementation.

This result provides strong evidence that the fundamental function of VMP1 as an ER-localized lipid scramblase is evolutionarily conserved. It also supports the use of T. gondii as a comparative experimental system for investigating VMP1 biology that may be difficult to dissect directly in *P. falciparum*.

Nevertheless, conservation of molecular function should not be interpreted as proof that every downstream phenotype is identical between the two parasites. *P. falciparum* and *T. gondii* have substantially different life cycles, host-cell environments, developmental stages, and specialised cellular structures. Therefore, comparative findings should be used to generate and test hypotheses rather than to directly transfer all *T. gondii* observations to malaria parasites.

5.5 VMP1 in Other Apicomplexans

VMP1-related proteins have also been identified in other members of the Apicomplexa, including parasites belonging to genera such as Cryptosporidium, Babesia, Eimeria, Theileria, and Neospora. Comparative analyses reported sequence identities of approximately 34.5–83.3% among apicomplexan VMP1 homologues, indicating substantial conservation within the group (Reddy et al., 2025).

The presence of conserved VMP1 homologues across these diverse parasites suggests that regulation of ER lipid distribution may represent an ancient and fundamental feature of apicomplexan cell biology. However, direct functional evidence remains much more limited outside T. gondii and P. falciparum. Future comparative studies could determine whether VMP1-dependent lipid scrambling is universally required for secretory-organelle biogenesis among apicomplexans or whether individual parasites have evolved lineage-specific functions.

5.6 How Related Parasites Help Explain VMP1 Biology in Malaria

The study of VMP1 in related apicomplexans provides several important insights into malaria parasite biology. First, *T. gondii* provides strong functional evidence. Genetic depletion experiments directly demonstrate that VMP1 is important for ER organisation, lipid-droplet homeostasis, secretory-organelle biogenesis, parasite development, invasion, and egress. These findings provide testable hypotheses for PfVMP1 (Reddy et al., 2025).

Second, functional complementation provides unusually strong evidence for conservation. The ability of PfVMP1 to rescue TgVMP1 deficiency indicates that the molecular activity of these proteins is sufficiently conserved to substitute across species.

Third, structural conservation supports functional interpretation. The conserved DedA domain, transmembrane organisation, sequence motifs, and predicted structures of PfVMP1 and TgVMP1 suggest that their lipid-scrambling mechanism is likely evolutionarily related (Reddy et al., 2025).

Fourth, comparative apicomplexan analysis can identify conserved therapeutic vulnerabilities. If VMP1-dependent lipid homeostasis proves essential across multiple apicomplexans, the VMP1 pathway could represent a broader parasite-specific vulnerability. Conversely, differences between species may reveal opportunities for selective inhibition of malaria parasites (Table 3).

Table 3: Established Evidence versus Interpretation

Observation	Current evidence	Interpretation for malaria
PfVMP1 is present in *P. falciparum*	Established	Confirms a VMP1 homologue
PfVMP1 contains DedA/multi-pass membrane features	Established	Supports conserved molecular architecture
PfVMP1 is an ER-localized lipid scramblase	Established experimentally	Strong evidence for a conserved core function
TgVMP1 is required for parasite development	Established experimentally	Provides a model for PfVMP1 function
TgVMP1 affects rhoptry/dense-granule biogenesis	Established experimentally	Suggests possible analogous roles in apicomplexans
PfVMP1 rescues TgVMP1 deficiency	Established experimentally	Strong evidence of functional conservation
PfVMP1 is essential for every *P. falciparum* life stage	Not established	Requires stage-specific experiments
PfVMP1 directly controls malaria invasion	Not yet established	Plausible but requires experimental validation
PfVMP1 is a validated antimalarial drug target	Not established	Promising but preliminary
VMP1 functions similarly in all apicomplexans	Proposed	Requires comparative functional studies

6. Role of VMP1 in Parasite Development and Survival

VMP1 appears to be an important regulator of **membrane homeostasis, lipid distribution, organelle biogenesis, and parasite fitness**. The strongest experimental evidence currently comes from *Toxoplasma gondii*, while direct functional studies in *Plasmodium falciparum* remain comparatively limited (Reddy et al., 2025).

6.1 Parasite Growth and Development

Conditional depletion of **TgVMP1** markedly impaired intracellular parasite development and reduced parasite fitness. Abnormal parasite morphology and defective development were associated with disrupted ER and lipid homeostasis (Reddy et al., 2025).

6.2 Intracellular Trafficking

VMP1-dependent membrane organisation is important for intracellular trafficking and secretion. TgVMP1 depletion impaired **microneme and rhoptry secretion**, indicating defective trafficking of proteins required for parasite invasion and egress (Reddy et al., 2025).

6.3 Organelle Maintenance

VMP1 disruption affected the formation and function of specialized secretory organelles, particularly **rhoptries and dense granules**. Altered ER organization and lipid-droplet homeostasis further demonstrate its role in maintaining parasite cellular architecture (Reddy et al., 2025).

6.4 Cellular Stress Responses

Because VMP1 regulates ER and lipid homeostasis, its disruption is expected to increase **membrane and ER stress**. However, the precise stress-signalling pathways activated following PfVMP1 depletion remain insufficiently characterized and require further investigation.

6.5 Replication

VMP1 depletion in *T. gondii* reduces normal intracellular development and therefore compromises parasite proliferation. Whether PfVMP1 is directly required for asexual replication of *P. falciparum* remains to be experimentally established (Reddy et al., 2025).

6.6 Host-Cell Interaction

VMP1 disruption compromises parasite **motility, host-cell invasion, and egress** in *T. gondii*. These phenotypes are consistent with defective secretion from rhoptries and micronemes, which contain proteins essential for host-cell interaction (Reddy et al., 2025).

6.7 Parasite Survival and Pathogenicity

The combined effects of impaired lipid homeostasis, organelle biogenesis, secretion, invasion, and egress substantially reduce parasite fitness. Thus, VMP1 represents a promising **emerging molecular target**, although its direct contribution to malaria pathogenicity and survival in *P. falciparum* requires further validation.

7. VMP1 and Parasite Pathogenicity

VMP1 may contribute to parasite pathogenicity by regulating **membrane homeostasis, secretory-organelle biogenesis, host-cell invasion, and intracellular survival**. However, direct evidence linking VMP1 specifically to malaria severity or clinical disease progression remains limited.

- **Parasite virulence:** In *Toxoplasma gondii*, VMP1 depletion significantly reduces parasite fitness, development, motility, invasion, and egress, indicating an important role in parasite virulence-related functions (Reddy et al., 2025).

Direct evidence in *P. falciparum* is not yet available.

- **Host-cell invasion:** TgVMP1 disruption impairs microneme and rhoptry secretion, resulting in defective host-cell invasion. Since *Plasmodium* also depends on specialised secretory organelles during erythrocyte invasion, a similar role for PfVMP1 is **plausible but remains to be experimentally demonstrated** (Reddy et al., 2025).
- **Intracellular survival:** VMP1-dependent maintenance of ER and lipid homeostasis appears essential for parasite cellular integrity. Loss of TgVMP1 compromises intracellular development and survival. **Whether PfVMP1 directly controls intracellular survival requires further study.**
- **Disease progression:** No direct evidence currently demonstrates that VMP1 determines malaria severity, parasite load, or clinical disease progression. Its possible contribution through parasite growth and host-cell invasion remains a **hypothesis**.

- **Transmission potential:** VMP1 could potentially influence transmission by affecting parasite development and sexual stages. However, **direct experimental evidence connecting VMP1 to gametocyte formation, mosquito infection, or transmission is currently lacking**.

8. Conclusion

VMP1 has emerged as an important **ER-associated membrane protein and lipid scramblase** involved in membrane organisation, lipid homeostasis, organelle biogenesis, intracellular trafficking, and parasite fitness. Evidence from *Toxoplasma gondii* demonstrates that VMP1 disruption impairs parasite development, secretory-organelle function, host-cell invasion, and egress, highlighting its biological importance (Reddy et al., 2025).

In *Plasmodium falciparum*, the conservation of VMP1 structure, ER localisation, and lipid-scrambling activity suggests a potentially important role in parasite survival and development. However, its precise effects on **malaria pathogenicity, replication, transmission, and disease progression** remain to be established experimentally. Therefore, VMP1 represents a **promising emerging molecular target**, but further genetic, biochemical, structural, and pharmacological studies are required to validate its potential for antimalarial drug development.

Overall, VMP1 may provide a novel link between parasite lipid homeostasis, organelle function, and survival, offering new opportunities for understanding and targeting apicomplexan parasites.

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