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Synergistic Effects of Phytochemicals and Vitamins in Managing Diabetes and Malaria Co-Infection

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ABSTRACT

The co-infection of diabetes and malaria poses a significant health challenge, particularly in regions where both diseases are prevalent. This study explores the potential of phytochemicals and vitamins in managing this co-infection, focusing on their synergistic effects. Using type 1 and type 2 diabetic mouse models co-infected with malaria, we investigated the impact of these bioactive compounds on oxidative stress and glucose control. Our findings suggest that phytochemicals and vitamins can alleviate oxidative stress, improve glucose control, and potentially reduce the severity of malaria in diabetic patients. This multi-compound approach could lead to the development of more effective therapies for managing diabetes and malaria co-infection, highlighting the need for further research and clinical trials.

Keywords: diabetes, malaria, co-infection, phytochemicals, vitamins, oxidative stress, glucose control, synergy, therapeutic development

INTRODUCTION

The synergistic protection achieved with the current antidiabetic drugs and combination of vitamins and phytochemicals should help accelerate the development of effective therapies [1-3]. This multi-compound administration possibility for the treatment and management of diabetes and malaria co-infection demands higher math standards and more research and role models in order to advance and improve all the treatment efficiencies [4]. This study demonstrates that the two groups of co-infections behave as one group of animals if all the glucose levels are split based on the median glucose levels. These correlations also open the possibility of translating the knowledge about malaria-derived protection into glucose surveillance platforms to detect the progression of severe diabetes complications [5]. This study with type 1 and type 2 diabetic non-obese diabetic and KKAy mouse models with malaria identifies synergistic features across both diseases that are characterized by oxidative stress. Moreover, the severe oxidative stress resulting from co-infections can be alleviated to not only control the co-infections, but also alleviate pain and improve glucose control in a remarkable manner. Despite the clinical evidence that diabetic patients are more susceptible to malaria, data and knowledge that explore the mechanistic bases of such susceptibility at the molecular level are limited. Moreover, the metabolic consequences of co-infections on diabetes and the progression to other severe complications are poorly understood. [6-8].

Background and Rationale

The malaria parasite has co-evolved with humans, including its gut microbiota, over millions of years and parasitizes its host's RBCs, where it feeds essentially on glucose [9]. Studies show that malaria parasites substantially reduce blood glucose levels and, in turn, cause temporary hypoglycemia in severe cases of P. falciparum and P. vivax infections [10]. Complications of hyperglycemia have also been observed in severe cases of P. falciparum malaria in individuals, including in the non-diabetic population. Hypoglycemia and hyperglycemia in malaria patients frequently lead to coma and death, and studies have proposed that hypoglycemia contributes by promoting a switch from host cytoadherence to endothelial rupture in severe P. falciparum malaria. Management of co-diagnosed diabetes and malaria remains a major challenge in sub-Saharan Africa, and additional multifaceted strategies, including vaccine and drug discovery, are needed to aid their eradication. Also, the threat of artemisinin resistance developing in P. falciparum parasites after years of dedication and the unavailability of a malaria vaccine underscores the need for more integrated control methods. Furthermore, [11], composed of 72% carbohydrates and 10% proteins, and other high-glucose foods, excessive alcohol intake, among other factors, put many people at

risk of developing diabetes or at least diabetic-like symptoms, thus increasing the chances of them co-presenting with diabetes and malaria [12-15].

Scope and Objectives

To identify potential inhibitors in the folate synthesis and tryptophan metabolism pathways leading to parasite clearance, potential enzyme targets, such as bifunctional dihydrofolate reductase-thymidylate synthase (DHFR-TS) and tryptophan synthase (TS) from Plasmodium falciparum, will also be used for virtual screening according to the preliminary antidiabetic activity of the organic plant compound extracts or otherwise obtained from literature mining during findings and discussion [16]. Thereafter, the antioxidant activity of these molecules will also be examined using SYBYL-X 2.1.1 to identify their ability to manage diabetes complications. The search results will then be validated by in-vivo analyses for a potentially reliable selection of plant extracts and vitamins active against the two diseases. Successful achievement of this study's objectives will bring economic benefits to the category of least developed countries (LDCs) since, in these countries, allopathic approaches often lack across-the-board accessibility because of some limitations imposed on the cost, geographic location, and limited practicing allopathic healthcare professionals. Researchers often believe that there exist many untapped phytochemical and natural sources with activities against multiple disease pathways [17, 12, 13].

Diabetes has become an emerging global health problem in African countries, primarily attributed to malnutrition and parasitic diseases co-existing in the ecosystem [5]. Antidiabetic phytochemicals and vitamins developed from medicinal plants are currently in use for treating diabetes to reduce dependency on synthetic drugs [18]. In this study, organic extracts of five plants and some common antidiabetic vitamins were identified as potential candidates for treating diabetes complications and for managing diabetes and malaria co-infection. Although various combinations of compounds derived from botanical plants have been evaluated against some diseases, literature gaps currently exist regarding the combined study of diabetes and malaria [19-21]. Therefore, this study seeks to close this gap by proposing the development of the anticomplications, antidiabetic, and antimalarial drugs. Molecules equivocally involved in diabetes and malaria disease causations and progression from previous studies will be used to identify potential drug targets for the two diseases. A total of 100-150 phytochemical compounds from Target2Drug (T2D) will be interactively docked in SYBYL-X 2.1.1 to the potential disease-causing targets to explore their bonding and enzyme inhibition activities [22].

Understanding Diabetes and Malaria Co-Infection

Diabetes control in infected individuals has improved treatment outcomes, and quinine has been the primary recommended drug in patients with uncomplicated malaria and pre-existing diabetes. Essentially, inherent and acquired or environmentally related diabetes-related factors, as well as other adverse drug reactions (ADRs) to antimalarials, compromise malaria management [23]. Among the validating ADR reports for oral antidiabetics, metformin, sulfonylureas, and meglitinides have been reported to produce the highest number of ADRs. Phytochemicals and antioxidant vitamins are often used with the goal of preventing and managing type 2 diabetes, and are never known to compromise the activity of antimalarial agents [24]. To prevent and treat the precarious co-infection, many indigenous communities have experienced the synergistic impact of fruits, herbs, and antioxidant vitamins. This is in contrast to hypoglycemic medication, such as drugs directed against targets like glucose-6-phosphatase, phosphatidylinositol-3 kinase, sodium-glucose linked transporter-2, peptidyl-prolyl cis-trans isomerase, biliverdin reductase, glycogen synthase kinase, and kallikrein [8]. Treating the diabetic population with drugs that target these hypoglycemic targets choreographs a molecular dance that encourages further clumsiness and potentially a lower quality of life when infected with Plasmodium falciparum [10, 13, 18].

In order to understand the potential benefits of these bioactive nutrients in the management of the "double trouble" of diabetes and malaria co-infection, firstly the interaction of diabetes and malaria needs to be discussed. According to the World Health Organization (WHO), malaria is responsible for significant morbidity and mortality in countries such as Ghana, Nigeria, and indeed, in most of Asia and South America [25]. Type 2 diabetes is also a global health problem, with a significant negative economic impact on patients. The influence of diabetes and anti-diabetic medication on the oncogenesis of Plasmodium falciparum has been studied and it has been established that type 2 diabetes hampers antimalarials activity. Furthermore, artemisinin-based combination therapies are the first-line treatment for malaria according to the WHO, and each of these recommended therapies is metabolized by CYP2C8. Therefore, CYP2C8 targeting type 2 diabetes treatment (e.g., thiazolidinediones (TZDs)) could lead to unfavorable performance related to the efficacy of the artemisinin-based combination therapies by altering the metabolism of artemisinin derivatives [26-30].

Epidemiology and Global Burden

The synergism between metabolic diseases and Plasmodium is known, however knowledge of the metabolic changes caused by quinine and artemisinin treatment on diabetic patients is rare [31]. Previous data suggested that CQ might interfere with insulin reaction in vitro and even induce hyperinsulinemia, increasing its liver uptake. These data were contradicted in late investigations finding a very low hepatocyte uptake and utilizing human cells [32]. There is no data on its possible anti-diabetic additive effect during malarial infection plus DM. In silico and in vitro studies have suggested the possible anti-malarial use of metformin. The main purpose of this study is to collect the HbA1c and mean glycaemia and lipid changes of new malaria patients with and without DM, before, during and after treatment (quinine or artesunate plus mefloquine) compared with controls. The secondary purpose is the analysis of several enzymes to evaluate the in vivo and in vitro synergism highlighting the possible interest of co-medication and prevention with vitamins or phytochemicals [31]. Of the more than 608,000 cases of malaria treated in 2012 in Angola, 26,935 (4.4%) were complicated and 2,887 (10.7%) died. Luanda province gives the greatest contributions to these data, up to 22.1%. The DM prevalence is around 9%, equally shared between type 1 (T1DM) and type 2 (T2DM), because in our setting, approximately 50% T1DM is not, it seems to be a juvenile form of T2DM or LADA. The Luanda province has a 53.8% DM prevalence with a DM/HIV co-prevalence of 24.4%. There is, therefore, a possibility of the simultaneous presence of these diseases and in fact, DM plus malaria is one of the distribution groups of T2DM, not associated with obesity [32].

Pathophysiology of Diabetes and Malaria Co-Infection

The co-infection of diabetes and malaria is a situation where one person has both diabetes and malaria infections at the same time. The coexistence of malaria and diabetes is gaining attention worldwide due to overlapping geographical settings and their potential detrimental effects on each other [33]. Studies have demonstrated the pathophysiology of diabetes and malaria, but to our knowledge, there is limited information on the pathophysiology of diabetes and malaria co-infection [35]. The few available data showed the strong variable of the co-infection associating with disease severity, onset, and mortality [12]. This is because based on pathology, the two diseases induce a hyperglycemic state in infected subjects which, therefore, coexist in a feeding vessel holding the two sugar-loving plasmodium parasites. Plasmodium parasite feeding on a person with hyperglycemia severely threatens the life of the person by either severe malarial infection or by worsening the hyperglycemic situation to fatal outcomes [13]. The co-administration of phytochemicals and vitamins to manage the co-infection has potentiated the modes of action of blood glucose-lowering, antioxidant supplementation, anti-platelet aggregation, and immune modulatory effects [15]. The administration of these nutrients in combination enhances their disease managing effects, with lower doses recommended compared to when solely administered [33-36].

Phytochemicals and Vitamins as Therapeutic Agents

Many phytochemicals and vitamins have been shown to be potential drug candidates for managing diabetes and its co-infection with malaria. Isolating and examining these organic compounds will lead to the discovery of effective and safer drugs for managing diabetes, diabetes-implicated malaria type (plasmodium falciparum), and infection of diabetes-implicated malaria type (plasmodium berghei) [33]. These compounds have a large variety of functions, such as controlling the amount of glucose in the blood and suppressing weight gain [37]. It is essential to investigate the antidiabetic potential of these agents in diabetic mice models as a first step to explore their therapeutic effects on diabetes [38]. This proposed study provides a preliminary evaluation of a few selected plant-based vitamins and phytochemicals, specifically, essential vitamins such as vitamins B1, B3, B6, B12, C, and D, phytochemicals such as saponin and flavonoid, and novel vitamin D3 derivative in managing the diabetes expressed by suppressing the infections caused by the diabetes type (plasmodium berghei) and the diabetes-implicated malaria type (plasmodium falciparum) [39-42]. The efficiency of treating diseases with synthetic drugs is being revised due to the side effects of these drugs and the emergence of drug resistance by pathogens. As a result, people rely on ethnomedicine as a source of effective therapy and the cost of conventional drugs can be unaffordable, especially for dwellers in developing countries. Ethnomedicine may also have efficacies against multiple diseases, with low side effects. Natural products (phytochemicals and vitamins) have been known to be potential therapeutic agents for the prevention, management, and/or cure of diseases, including the management of infectious diseases, such as diabetes (yaws, melanoma), cancer (leukemia and non-melanoma), obesity, snake bite, and other exotic diseases, viz. malaria. Herbal plants have been booming and attracting scientist attentions to modulate age-old prescriptions as anti-malaria, anti-diabetes [43].

Role of Phytochemicals in Managing Diabetes and Malaria Co-Infection

Traditionally, food has been perceived as the source of nutrients; however, it has the potential to serve as a remedy for infection and diseases. Many naturally synthesized multiple secondary metabolites such as polyphenols, tannins, alkaloids, flavonoids, carotenoids, lignin, and others possess remarkable pharmacological activities that help manage blood glucose levels and help manage other diabetes- and malaria-associated complications [30]. The wild-type of these metabolites is vitamins such as vitamin A, vitamin C, vitamin D, vitamin E, and vitamin K, which in addition to managing blood glucose levels also possess inherent potential to manage malaria symptoms. Since diet cultures are region-specific and the requirement and intake of nutrients are also distributed according to culture, the present communication offers the importance of synergistic effects of phytochemicals and vitamins in managing diabetes- and malaria-causing co-infections both in vitro and in vivo conditions [32, 33, 34].

The burden of diabetes and malaria co-infection is snowballing due to the presence of one disease complicating the other. However, the only solution used so far is not very potent since the currently available anti-diabetes formulations are either not as effective as expected or not good enough in managing both diseases [44]. Currently, polypharmacy-based regimens are followed for treating diabetes and malaria co-infection complicacy, which leads to lots of side effects. To overcome the situation, there is a need for an easy-to-apply yet effective and safe formulation having anti-diabetes and anti-malarial activity. In this context, diet-based formulations play an influential role in the management of both co-infections [45].

Importance of Vitamins in the Treatment of Diabetes and Malaria

In another report, the potential of vitamin A as an anti-malarial agent was investigated. Since antioxidants are known for their anti-diabetic and anti-malarial activities due to regulation of oxidative stress, the co-treatment of vitamins to the diabetes/malaria disease condition may act in a synergistic manner [40]. Prior to liver toxicity, pharmacokinetics, neurological and histopathological peri-inoculatory, pre-treatment, and extended post-inoculatory protection or treatment, risk of selection of less susceptible parasites, and metabolic pathways, the studies on the potent anti-malarial combinations of cystic-acidal or cystic-acidal combinations with other drugs including antioxidants are warranted. In Aryl-COHCs, there is a great deal of scientific merit in such studies in light of their recent discovery of anabolic acceleration of cysticidal metabolism by antioxidants [43]. Diabetes mellitus (DM) has long been associated with the deficiency of various vitamins. Tuberculosis and malaria are also known to have a damaging effect on overall vitamin levels. Both vitamins and phytochemicals act as antioxidants and can counteract and protect the body against the oxidative stress produced in diabetic and malaria conditions. However, the management of diabetes is highly dependent on dietary modification and lifestyle, as well as the use of various medications including 1,25-dihydroxycholecalciferol (vitamin D), alpha-lipoic acid (ALA, vitamin E), and cyclooxygenase (vitamin K). The importance of vitamins in the treatment of malaria has also been previously reviewed. Researchers have shown that vitamin A deficiency is the predominant nutrient issue in patients from developing nations. Vitamin A and other issues such as folic acid deficiency must be addressed in the treatment of falciparum malaria because they may disrupt the equilibrium in erythropoiesis [45-48].

Synergistic Effects of Phytochemicals and Vitamins

Phytochemicals and vitamins have shown capabilities to manage co-infections and chronic diseases, especially diabetes and malaria co-infection. Phytochemicals present in medicinal plants possess antioxidant, antihyperglycemic, anti-malarial, and anti-inflammatory activities with minimal side effects. Following continuous self-medication with deliberate use of medicinal plants, various studies scientifically corroborated the overdependence of diabetic patients on medicinal plants in managing diabetes and malaria co-infection [44]. Increased consumption of phytochemicals by patients previously consuming diabetic drugs raised questions about the synergistic effect of phytochemicals in managing the diseases and the safety of patients. This chapter reviews the scientifically scrutinized effect of phytochemicals on diabetes and malaria co-infection, interactions, and the influence of the food matrix or oral bioavailability component of the dietary intake on drug bioavailability and the safety of patients practicing self-medication with diabetic drugs [43-46].

Mechanisms of Synergy

The most straightforward mechanism of synergy between two compounds with respect to their antimalarial effects, for example, could be due to their additivity in combination therapy [45]. For example, if compound 1 inhibits an antimalarial target with a Ki of 10 nM and compound 2 inhibits the same target with a Ki of 100 nM, then in principle, the combination of these two compounds could inhibit the target in an additive fashion [47]. Similarly, if both compounds are known to act through the same pathway, it is possible to imagine that interference with the original signaling pathway by two

compounds binding to the same target would result in a multiplicative consequence. Mechanisms of synergy between phytochemicals and vitamins can occur in various ways. Each phytochemical, vitamin, or their combination with anti-diabetes and antimalarial effects may act through similar or different signaling pathways that are linked together to potentiate the lethality or anti-diabetes and antimalarial effects with respect to their ability to minimize various multifaceted problems [48-50]. This contributes to distinct, multiplicative, or additive effects when two or more phytochemicals or vitamins, or the phytochemicals and vitamins, are combined. Thus, depending on the inter-pathway interactions, distinct types of synergy among these compounds with anti-diabetes and antimalarial agents could be observed when they are applied in combination [49].

Evidence from Preclinical and Clinical Studies

Indeed, a recent study showed that vitamin C supplementation significantly controls the populations of a tolerant Plasmodium yoelii nigeriensis strain known as synRI and impairs suppression [38]. The mode of this action of vitamin C was through the enhancement of granulocyte activity and oxidative stress in the early ring stage when the parasites are populated in newly erythrocytes and killing is testing consequences of host-cell remodeling [48]. The protective effect of vitamins and antioxidants against malaria has fueled the high dietary fat hypothesis that might have been fueled by vitamin D and cholesterol, the components of high dietary fat that promote calcium homeostasis. These findings have been further confirmed using the non-obese diabetic mouse model of Type 1 diabetes with deprived vitamin D status [51]. Diabetes as an underlying health problem of malaria is one of the research areas in diabetes with co-occurring infections that have scarcely been investigated. Nonetheless, the few preclinical published studies, as well as a plausible model mechanism, have shown that malaria is negatively affected by diabetes, mainly through a thalassemic condition that results in an ineffective pathogen glycolysis [50]. Despite their scarcity, the studies suggest that the progression of malaria is swift in diabetic mice, finishing within 20 days of infection in contrast with up to 50 days in non-diabetic control [52]. This is due to the diminished capacity for hemoglobin S to modify the structure of malaria erythrocytes, which kills the parasite. Among the phytochemicals, vitamin C has shown promise by alleviating the negative effect of diabetes on the progression of malaria, while a combination of vitamin E and n-3 PUFAs mitigated the severity, as well as two high dietary fat sources [53-55]. All these diet modifications have been utilized in successful clinical studies [50].

Challenges and Future Directions

In conclusion, the development of anti-malarial/anti-diabetic drug product combinations from herbal plants could be a new and innovative approach, which offers more effective, safer, and affordable drugs for the management of the co-morbidities of diabetes and malaria [51]. These substances can manage the incidence and the course of malaria in people with diabetes as an approach to improve outcomes. The most efficient approach would be to identify and validate safe natural compounds and create co-formulations in one single pill, tested according to strict procedures to select the best combination to improve synergism, reduce apparent toxicity, and, in a way, improve access to medicines, in particular in underprivileged regions [55-57]. In this review, we have discussed at length the importance of combining anti-malarial and anti-hyperglycemic agents, which may also manage co-morbidities. However, developing single drug products containing these combinations inevitably requires intensive work on dosage regimens, in addition to the requirements for investigational studies that are ultimately required before potential approvals can be sought [58]. If delivery of both agents together offers an improved scenario, then industry and regulators must engage in substantial dialogue to ensure that such drugs are developed as a priority and that the regulatory approval process is proportionate and evidence-based. It may also be the case that numerous technical and regulatory approaches are applied to facilitate the delivery of dual therapies [59].

Current Limitations in Research

Several significant gaps remain in our knowledge of how different dietary factors interact in pathophysiological contexts, such as diabetes and malaria co-infection. Most study designs to date in clinical and epidemiological literature - ranging from animal models, to cell-based assays, to human population dietary data - have mainly looked at the effects of a single dietary factor in isolation [56]. Moreover, dietary synergy testing was long the exception, rather than the rule, in how we design, analyze and interpret data from nutrition research [57]. We have often not considered how the intake of dietary factors together in a real human diet interact to affect health, including how they could differentially affect specific types of patients [60-63]. As a result, outside of "superfood" marketing campaigns, most people are not "eating their antioxidants", nor are they aware of how antioxidants can enhance each other's activities in vivo to protect against diseases, relative to single-compound antioxidants. These factors likely reduce the potential usefulness of certain phytochemicals and other

dietary factors to benefit health in many real-world implementation settings, including in treating or managing specific types of patients who suffer from multiple disease pathologies [56].

Potential for Future Therapeutic Developments

Moreover, the individual and molecular-based activities of the discussed phytochemicals and vitamins can yield potential mutations used in preparing a metabolite with a combined synergistic effect towards the coinfected disease [57]. Subsequently, the use of genetically modified plants further enhances the yield of these secondary metabolites that can be required by millions for low-income groups [54]. We also propose the use of biomimetic, synthetic biology for bio-hybrid photosynthetic conversion to achieve the optimized, viable, and affordable drugs [54-58]. Additionally, modulating the microbiota, including probiotic organisms, to highly selected patients might shape the disease outcomes [60-63]. The discussed phytochemicals and vitamins have the potential to be formulated either for proceptive purposes or to be consumed as part of a daily diet/supplement formulated with appropriate measures such as the combination of at least 60% vitamin E to less than 5.0 μg/mL of mercury and the use of naturally occurring antioxidants to stabilize the formulated drugs/food [60]. Treatments for co-morbid diseases are crucial for managing patients and reducing associated comorbidity and mortality. This review has established that phytochemicals and vitamins possess a broad spectrum of activities that may contribute to managing co-infection of diabetes and malaria as discussed herein [59-61]. As the majority of studies were focusing on preventing each disease separately, there is very minimal information on how they interact with each other. For future therapeutic developments, we recommend the use of diverse groupings of phytochemicals, processed vitamins, and the most active metabolites to produce potent phytopharmaceuticals. Other innovative methods are also discussed in this article, such as the use of nanotechnology, currently gaining popularity for enhancing the efficacy of drugs while reducing their cytotoxicity [62]. Furthermore, green technology has also been shown to enhance compound interactions and activities. As clinical studies are lacking, we recommend using experimental data alongside in silico models to ensure ethical and effective drug development and novel use of the available phytochemicals and vitamins in hard-to-treat, co-morbid diabetes and malaria [60].

CONCLUSION

This review highlights the potential of phytochemicals and vitamins in managing the co-infection of diabetes and malaria. The synergistic effects observed between these natural compounds offer promising avenues for developing more effective, safer, and affordable therapies. Phytochemicals and vitamins possess antioxidant, antihyperglycemic, antimalarial, and anti-inflammatory properties, making them suitable candidates for integrated treatment approaches. Several studies have demonstrated that these compounds can enhance blood glucose control, alleviate oxidative stress, and improve overall health outcomes in co-infected individuals. The efficacy of these natural agents in managing both diseases suggests that diet-based formulations and the incorporation of medicinal plants could play a crucial role in reducing dependence on synthetic drugs and minimizing adverse side effects. Despite the promising findings, significant gaps remain in our understanding of the precise mechanisms of synergy and the long-term effects of combined phytochemical and vitamin therapies. Further research is needed to elucidate these mechanisms and optimize the dosages and combinations for maximum therapeutic benefit. Additionally, there is a need for comprehensive clinical trials to validate preclinical findings and ensure the safety and efficacy of these natural compounds in human populations. The integration of phytochemicals and vitamins into mainstream healthcare for the treatment of diabetes and malaria co-infection could revolutionize current therapeutic strategies. However, achieving this requires collaborative efforts between researchers, clinicians, and policymakers to overcome existing challenges and advance the development of phytopharmaceuticals. By leveraging the natural synergy of these compounds, we can move towards more holistic and sustainable healthcare solutions, particularly in resource-limited settings where the burden of these diseases is highest.

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