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EFFECT OF A POLY-PILL OF METFORMIN, ARTESUNATE AND ESOMEPRAZOLE LOW-DOSE (MEALD) COMBINATION IN PREVENTION OF MALARIA AND SELECTED METABOLIC SYNDROME CRITERIA

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ABSTRACT

Malaria-induced attenuation of the insulin signalling pathway may be important in the aetiology of T2DM, while T2DM has been linked with increased malaria risk. AMPK activators, of which metformin, artesunate and esomeprazole are examples, down-regulate malaria-induced inhibition of AMPK, upregulate host immunity and may inhibit the spread of drug resistance in malaria. They also attenuate all stages of malaria parasite life-cycle. The long clinical duration of action of esomeprazole and the accumulation of metformin in erythrocytes may acquit them satisfactorily as combinatorial agents with artesunate which has a short duration of action. In the present report, the effect of the combination of metformin (500 mg daily with no interruption), esomeprazole (10 mg daily; intermittent) and artesunate (12.5 mg daily; intermittent) low-dose (MEALD) combination was compared to that of metformin alone in the attenuation of selected metabolic syndrome criteria in adult men. Also, the differential effects of the drug combination and metformin alone on parasite clearance and fever recrudescence were compared in adults. Results show that the MEALD combination was more significantly effective ($P < 0.05$) in reducing glucose levels and other selected metabolic syndrome criteria and in effecting parasite clearance and preventing parasite recrudescence over 18- month period than the metformin alone. Present report highlights that the MEALD combination deserves further study in a larger sample size. This would define its role in addressing both malaria drug resistance and the diabetes-malaria connection.

KEYWORDS: Metformin-artesunate-esomeprazole; Malaria parasitaemia; Metabolic syndrome.

INTRODUCTION

The rising prevalence of type 2 diabetes mellitus and the intolerable overwhelming burden of malaria impact negatively on healthspan and lifespan in Sub-Saharan Africa (SSA)which account for 90% of all global deaths due to malaria.[I] Report by WHO notes that diabetes prevalence has risen faster in low- and middle-income countries than in high-income countries and now accounts for about 8.6% of all deaths in adults.[2,3] Current prevalence in Nigeria may be 8%-10%, far above the <1% in 1960.[4,5] High glucose levels and type 2 DM has been noted to increase mosquito-induced malaria transmission and the risk of malaria infection.[6,7,8] At the same time, malaria-induced oxidative stress may attenuate the insulin signalling pathway and upregulate diabetes risk.[9,10] The emerging epidemic of type 2 diabetes and the endemic malaria have been referred to as the double burden of Africa,[3] who noted that the malaria burden may now be shifting to the older age-groups. The probable import of this seeming spectre of a reciprocal association between malaria and type 2 diabetes mellitus is that attempts at prevention of malaria and of malaria resistance to chemotherapeutic agents must go *pari passu* or in tandem with efforts at prevention and treatment of type 2 diabetes.

Role of immunity in malaria

Non-specific and the specific immunity response to malaria are the most important contributors to parasite clearance from peripheral blood.[11,12] In endemic areas, immunity enhances therapeutic responses to malaria, helping to clear drug-resistant asexual parasites and gametocytes.[13]

Acute and chronic malaria drives T cells ($CD4^+$T cells and $CD8^+$T cells) to exhaustion via the Treg induction of the inhibitory proteins cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed cell death ligand-I (PD-I) and lymphocyte activation gene-3 (LAG-3).[14] The apparent failure of vaccine application in malaria may be most likely due to this immune exhaustion. This scenario may be compounded by the reported glycosylation of the immune cells in diabetes leading to their exhaustion and

desensitization.[15] Combined blockade of PD-I, CTLA4 and LAG3 increases numbers of $CD4^{+}T_{FH}$ and germinal centre B cells along with higher antibody titres to control blood- stage parasites.[14,16,17,18]

Chemotherapy in malaria

i. Metformin

The accumulation of the anti-diabetic metformin in erythrocytes and an attendant elimination half-life of 18.5 to 31.5 hours makes it a possible suitable partner drug with artesunate. Metformin has been shown to reduce *Plasmodium falciparum* prevalence and to exhibit synergistic effects with atovaquone.[7,19] Very recently, it has been reported to decrease the expression of CTLA-4, PD-I and LAG-3. Metformin thus promotes $CD4^{+}$ T cell function, inhibits granulocytic myeloid suppressor cells, increases secretion of protective antibodies and clears blood-stage malaria.[20,21,22,23] There is enhanced half-life of ring- stage sporozoites and an upregulated unfolded protein response (increased proteasome activity) in the emerging K13-associated artesunate resistance.[24] Non-toxic proteasome inhibitors have been credited as able to prevent malaria parasite resistance including K13 mutation-associated resistance, and to synergise with artesunate against all stages of sensitive and resistant strains of *Plasmodium falciparum.*[25] The AMPK activator, metformin, also inhibits plasmodial proteasome and this may explain its attenuation of survival of blood-, liver- and transmission- stages of the malaria parasite.[26,27,28,29,30,31] Additionally AMPK activators attenuate host myosin I heavy chain kinase- (MIHCK-) or P-21 activated protein kinase- (PAKI-) mitogen-activated protein kinase kinase I- (MEKI-) signalling pathway important in survival, proliferation and infection of malaria parasites.[32,33,34,35] Furthermore, AMPK activators upregulate the tumor suppressor protein, p53 transcription factor and attenuate liver-stage parasitaemia.[36] AMPK activators also inhibit HIF-alpha, enhance autophagy and B-oxidation of fatty acids necessary for attenuation of liver-stage infections.[37,38,39,40] Examples of other safe AMPK activators or PAKI blockers are curcumin, resveratrol and the King of Bitters (andrographolide) which are used for malaria, type 2 diabetes mellitus, bacterial infections, cancers and neurodegenerative diseases.[32,41]

ii. Esomeprazole

Although the half-life of esomeprazole is 51.0 minutes (0.85 hours), its clinical duration of action is 24-72 hours.[42] Esomeprazole's covalent binding or its sulfenamide metabolite to a *P. falciparum* H^{+} - ATPase may prolong its *antimalarial effect*, making it another suitable partner drug with artesunate. Similar to omeprazole, its S-enantiomer, esomeprazole has been noted in several experimental paradigms to exhibit liver- and blood-stage anti-malarial activity against ring-stage trophozoites, early trophozoites, mature trophozoites and schizonts.[43,44,45,46] It suppresses chloroquine resistance, inhibits multi-drug resistance proteins and may exhibit effects on Plasmodium falciparum's N^{+} -ATPase pfATP4 with probable similar potency to the spiroindolones. Its combination therapy with artesunate exhibits additive effects and prevents/reverses malaria drug resistance.

Esomeprazole, an AMPK activator, may increase insulin release via gastrin and synergise with GLP-1 receptor agonists.[47,48]

iii. Artesunate

The elimination half-life of artesunate is 0.36-1.2 hours, while that of its metabolite dihydroartemisinin is 0.5-1.5 hours.[49] Artesunate rapidly kills ring-form trophozoites, preventing their further development to mature trophozoites which cytoadhere, sequestrate and then evade the immune mechanisms. The actions of the spleen in pitting drug-impacted parasites, mechanical filtration and antibody production complement the actions of artesunate. Delayed parasite clearance at Day 3 (72 hours) of initiating therapy or early treatment failure is a measure of artesunate resistance since the early parasitological response in combination therapies is determined largely by the artemisinin component. To prevent recrudescence, the malaria parasites that remain after exposure to the artemisinin component for two 48-hr asexual cycles of *Plasmodium falciparum* must be cleared by the slowly eliminated drug in partnership.[11,12] Extended use of the AMPK activator and proteasome inhibitor, artesunate, has been recommended for K13-associated malaria parasite resistance.[25]

Artesunate also enhances the insulin signalling pathway and may also enhance insulin transport across the blood-brain –barrier via endothelial nitric oxide.[50,51] It enhances brown adipose tissue (BAT) function and increases insulin release through augmenting or enhancing the amplifying pathways of insulin secretion mediated by eNOS, GABA-A agonists and preventing the DNA Damage Response-induced pancreatic β-cell apoptosis.[52,53,54,55,56]

Drug resistance in malaria

Presently, parasite resistance to antimalarial medicines has been documented in 3 of the 5 malaria species known to affect humans: *P. falciparum*, *P. vivax* and *P. malariae*. Anti-malarial resistance is defined as the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject *(WHO).* Artemisinin resistance is also defined as delayed parasite clearance following treatment with an artesunate monotherapy, or after treatment with an artemisinin-based combination therapy (ACT). The inclusion of a day 3 parasite count in routine studies provides a method for ruling out artemisinin resistance with a defined precision.[11,57] Parasitaemia at days 28 and 42 may be due to partner drug resistance/recrudescence or new infections and distinction is made by genotyping or PCR. Cure rates for ACT should not be less than 95%. Treatment failure is the inability to clear parasites from a

patient's blood or to prevent their recrudescence after the administration of an antimalarial. Many factors can contribute to treatment failure, including incorrect dosage, poor patient compliance, poor drug quality, and drug interactions and resistance. Most of these factors are addressed by therapeutic efficacy studies (TES).

Drug resistance imperils malaria eradication efforts

The steady appearance of *Plasmodium falciparum* resistance to many antimalarial medicines over the past several decades has since led malaria endemic countries to adopt artemisinin-based combination therapies where the half-life of the efficacious partner drug is not less than 24 hours (ACTs).[12] There are reports of probable and verified emergence of resistance to ACTs.[58,59] Protecting the efficacy of ACTs as the current first-line treatment for *P. falciparum* malaria is among the top global public health priorities. Multi-drug resistance (MDR) requires resistance to more than 2 operational antimalarial compounds of different chemical classes.

Factors favouring the emergence of drug resistance include monotherapy, strong drug pressure, exposure to suboptimal drug concentrations especially for drugs with long half-lives and fake drugs. Sulfadoxine-pyrimethamine elevate gametocytaemia and may favour transmission.[60]

Known resistance genes encoding for transporter proteins are pf^{CRT}, pf^{MDRI} (chloroquine resistance, incomplete cross-resistance to amodiaquine and inverse correlation between chloroquine and lumenfantrine resistance);pf^{CRT}, pf^{MDRI}; pf^{NHEI} (quinine resistance); pf plasmepsin (aspartic protease) 2 and 3 amplification, pf^{CRT} (resistance to piperaquine); pf^{MDRI} amplification (mefloquine); SNPs in cytochrome bci complex (atovaquone resistance); pf^{DHPS}, pf^{DHFR} (quick emergence of resistance to antifolates); pf^{MDRI}, mutation in the Ca^{2+}-ATPase pfATP6, the Na^{+} - ATPase pfATP4 for Na^{+} regulation in the parasite (artemisinins and spiroindolones resistance); mutation in Kelch-13-propeller region (primary factor in artemisinins resistance). K13-associated resistance has not been reported from Africa.[61,62,63] An association between pf^{CRT}, pf^{MDRI}; pf^{DHFR} and pf^{DHPS} genotypes/haplotypes has been reported.[64]

THE AIM OF THE STUDY

The sheer enormity of the malaria and type 2 diabetes burden in adults compels the need for effective drug or drug combinations as preventive. Present study was spurred by the finding that patient- volunteers on 500-1000 mg of metformin (Glucophage) for prevention of type 2 diabetes since 2013 subsequently had decreased incidence of malaria fever. The aim of this work was to compare the effects of low-dose metformin, esomeprazole and intermittent artesunate low-dose (MEALD) combination versus low-dose metformin alone on the prevention of malaria and selected metabolic syndrome criteria in adults.

METHODS

This prospective study was done at Department of Pharmacology, AAU, Ekpoma and Oseghale Oriaifo Medical Centre, Ekpoma. Patients's informed consent was obtained in writing and study was approved by the Ethical Committee of AAU's College of Medicine, Ekpoma and of Oseghale Oriaifo Medical Centre, Ekpoma. 12 adults of either sex participated in the study on the effects of metformin (500 mg daily) –artesunate (12.5 mg daily; intermittent)-esomeprazole (10 mg daily; intermittent) low-dose (MEALD) combination and calorie restriction on malaria and metabolic syndrome criteria. The combination was given for 3 months with a break of 3 months with only the metformin administered with no interruption. This intermittent administration prevented possible neurotoxic effects of the artesunate + esomeprazole combination; which may include light-headedness and swaying movements. The effects were compared to a similar number of volunteers who took low-dose metformin with calorie restriction alone; and to a third group that were on placebo with *ad libitum* feeding. Patients with early type 2 diabetes were included; but these continued with 1000 mg metformin daily. Volunteers were free of parasitaemia and fever before start of study. Before the start of the study, all participants were screened for malaria parasitaemia by Giemsa staining of thick (parasite density and species identification) and thin (definitive parasite species identification) blood smears. Positive cases were appropriately treated and there was satisfactory response to artesunate 4 mg/kg IM daily for 3 days + esomeprazole 40 mg daily for 3 days + metformin 750 mg daily for 3 days. On Day 3, less than 1.5% of patients were parasitaemic indicating no resistance to artesunate. By Days 28 and 42, less than 0.5% of patients were parasitaemic indicating no resistance to the partner drugs of esomeprazole and metformin *(WHO: Status report on artemisinin and ACT resistance. 2015*).

Exclusion criteria

Volunteers with heart failure, sever kidney and liver disease were excluded. Patients with chronic type 2 diabetes were also excluded.

Statistical analysis

Paired Student's t-test was used and one-way Analysis of Variance (ANOVA) applied to compare only two samples (t-test) or more than two samples (one-way ANOVA) followed by Duncan Multiple Range test (DMR) or the Tukey-Kramer Multiple Comparison Test as *post-hoc* tests. Data are presented as mean ± standard error of mean (S. E. M.); number of subjects used for each experiment (n) = 12). The difference was considered to be significant at $P < 0.05$

RESULTS

Table I: Effect of Metformin, esomeprazole and artesunate low-dose (MEALD) combination on incidence of malaria parasitaemia, fever and selected metabolic syndrome criteria.

		Control			Metformin			MEALD		
	Mouth	6	12	18	6	12	18	6	12	18
1.	Incidence of fever	1.20±1.6	2.60±0.5	4.23±1.8	0.50±2.1	1.10±3.2	1.10±5.1	0.4±1.2	0.2±1.6	0.50±0.80
2.	Incidence of malaria Parasitaemia	0.52±3.6	1.80±2.5	4.50±2.2	0.95±1.5	0.80±1.7	2.30±3.2	0.40±1.7	0	0
3.	BMI (m/kg^2)	26.0±1.9	27.2±2.2	31.6±5.6	24.0±2.1	23.0±1.6	23.2±2.2	24.0±2.1	22.1±1.8	22.0±2.3
4.	Glucose Level (mg/dl)	118.2±3.4	115.2±2.5	130.5±2.7	112.3±1.5	102.9±2.4	100.5±3.8	88.3±1.2	80.7±2.1	78.9±3.2
5.	Uric Acid (mg/dl)	8.80±0.6	8.90±1.3	9.85±1.6	7.50±1.9	7.30±2.0	7.10±2.0	6.80±0.6	6.40±0.9	5.75±1.1
6.	Respiratory tract infection	0.5±1.3	1.2±1.9	2.1±2.5	0.4±0.7	1.2±0.8	1.5±1.1	0.3±0.8	0	0
7.	Walking Distance (m)	480.6±5.7	460.3±6.2	450.4±8.9	482.5±4.2	500.3±3.6	530.9±8.9	601.9±4.6	606.6±5.2	608.6±4.8
8.	Number of Arthitic Pain exacerbations	2.4±2.0	5.6±3.1	6.6±5.1	1.7±2.1	2.5±3.6	2.3±2.9	0.9±2.7	0.5±2.8	0.5±3.9

Table I: The intermittent MEALD combination most significantly ($P < 0.05$) decreased the incidence of fever, malaria parasitaemia and the metabolic syndrome criteria of BMI, glucose and uric acid levels. It also most significantly increased the walking distance before fatigue and decreased the number of arthritic pain exacerbations.

3 volunteers withdrew from the study due to probable side-effects of dizziness and mild movement disorder. Present results (Table I) show that patients on the MEALD combination/polypill administration had significantly ($P < 0.05$) greater reductions over the low-dose metformin on incidence of fever and malaria parasitaemia over a 18-month period. They also had significantly greater reduction in the selected metabolic syndrome criteria of raised glucose, uric acid, BMI levels, exacerbations of arthritic bone pains and early fatigue on exertion. The MEALD combination also most significantly decreased the Blood Pressure (not shown). There was reduced incidence of respiratory tract infections, glaucoma and vision defects; and impulsivity-related accidents at work. All these indices are known to be possible metabolic syndrome criteria.

DISCUSSION

The number of under-5 children dying from malaria has halved since 2000 due to greater political commitment and funding to prevent and treat the disease (*WHO: World Malaria Report. 2013*). In spite of the above, malaria and malaria-associated infections are reported to still exert a significant toll on well-being and economic output of citizens of Sub-Saharan Africa. For example, investigators have noted that *Plasmodium falciparum*-associated malaria causes global immune defects with lower immunity to rhinovirus infections and invasive non-typhoidal Salmonella.[65,66,67] Importantly, the rising profile of (microscopic and sub-microscopic) malaria and type 2 diabetes as co-morbid illnesses and cause of reduced healthspan and lifespan in the SSA region is attracting attention.[6,7,68,69] Type 2 diabetes mellitus and malaria enhance cell replicative senescence and may additively attenuate anti-viral effect of the anti-senescence gene SIRTI.[70,71,72] Both diseases may activate the DNA Damage Response- (DDR)-HMGBI/2-NF-kappaβ- Senescence-Associated Secretory Phenotype-(SASP) pathway, induce telomere attrition, upregulate senescence-associated secretory factors such as MCP-I and may negatively impact type 1 interferons needed for anti-viral/anti-bacterial defense.[73] Non-toxic metronomic usage of AMPK activators such as metformin, artesunate and esomeprazole which may inhibit HMGBI and NF-kappa B upregulation in malaria infection could demonstrate anti-inflammatory and senolytic effects acting on the above pathway.[74,75]

The looming reality of a possible development of resistance to the ACTs in, or spread of K13-associated artesunate resistance to the SSA region calls for unwavering dedication to a search for probable safe options. For example, artesunate + azithromycin combination therapy has been found suitable as an efficacious and safe alternative in Asia.[76] The need for new remedies that may additionally quell the bourgeoning type 2 diabetes threat is compelling and glaring.

Present study that MEALD combination prevents malaria, type 2 diabetes is explainable at several levels. Most importantly, AMPK activators such as calorie restriction, metformin, artesunate and esomeprazole may enhance signalling via insulin receptor substrate$_{1/2}$($IRS_{1/2}$), inhibit *Plasmodium falciparum*-induced PD-I, LAG3 and CTLA4, attenuate the host upregulated PAK-MEK signalling pathway.[32] They also down-regulate the increased HMGBI-RAGE and HIF-α signalling axis but increase p53 protein during malaria infections.[36,37,38] These mechanisms serve to enhance immunity, decrease the immune cell exhaustion, increase parasite killing and sustain glucose homeostasis. These actions of MEALD combination are vital to parasite

clearance and prevention of complications during malaria infections.[14]

Metformin is a known anti-diabetic associated with inhibiting progression of pre-diabetes in the Diabetes Prevention Program(DPP) study.[77] Artemisinins induce insulin release at high glucose concentrations via GABA-A receptor while esomeprazole also enhances insulin release.[53] Esomeprazole and artesunate stand to synergise with low-dose metformin in glucose homeostasis and reducing malaria transmission, a key issue in resistance transfer. Metformin-Fe^{3+} interactive complex in the red blood cell of infected parasites inhibits the cysteine protease (falcipains-2, 3) that may promote insulin catabolism, and also inhibit haemoglobinase thus increasing insulin signalling and preventing haemoglobin usage by the malaria parasite.[78] The mechanism of metformin as anti-proteolytic and proteasome inhibitor is similar to curcumin's. Its inhibition of PAKI and PD-I which are upregulated in malaria, type 2 diabetes stands metformin at the cross-roads of malaria, bacterial/viral infections, type 2 diabetes mellitus, neurodegenerative diseases and cancers.[32,79,80]

Enhancement of the insulin signalling pathway, the PI3K-Akt-eNOS-PPAR-alpha pathway, mitochondrial biogenesis by metformin, artesunate and esomeprazole may decrease malaria transmission from the infected mosquito,[81] malaria parasitaemia, malaria- and type 2 diabetes-associated inflammation. These may also serve to attenuate PD-I/PD-4 expression in patients with type 2 diabetes and severe sepsis.[51,82,83,84,85]

Metformin, artesunate and esomeprazole inhibit MDR proteins and multi-drug resistance-associated protein.[86,87,88,89] As AMPK activators, they inhibit the parasite's proteasome and decrease the upregulated UPR implicated in artemisinin K13 mutation-associated resistance. Similar to artesunate, metformin shows additive effect with the proteasome inhibitor, bortezomib in inhibiting K13 mutation-associated resistance.[25,90] Proton pump inhibitors also prevent mutations and this may be useful in prevention of resistance emergence in malaria.[91,92] pf^{CRT} which is related to pf^{MDRI}has been termed a proton pump.[64,93,94] KEAP-I which is inhibited by esomeprazole, metformin and artesunate is identical to K13 involved in artemisinin resistance.[95,96] AMPK activators inhibit mTOR-dependent translations and which is dysregulated by sporozoites invasion of the liver thereby enhancing immune response in malaria, preventing mutations,[97,98] and even BBB disruption.[98] It may be note-worthy that the UPR may also be upregulated in obesity and insulin resistance.[100]

Esomeprazole, metformin and artesunate may decrease brain iron overload associated with type 2 diabetes, aging and inflammation-related neurodegenerative diseases such as Alzheimer's disease.[101,102,103] Increased iron trafficking in concert with uric acid and haemozoin may be associated with increased ATP release, NLRP3 inflammasome, NF-kappa B activation and telomere attrition which are commonalities in malaria and type 2 diabetes. They result in downregulation of insulin signalling, attenuation of immunity and increase risk of malaria, bacterial, fungal and viral infections.[104,105,106,107,108]

An elevated level of ATP has been recorded both in the extracellular environment and in the cytoplasm of host and malaria parasite.[34] Thus, downregulation of ATP by the AMPK activators calorie restriction, metformin, artesunate and esomeprazole may prevent ATP usage by hydrolysis essential in the actions of the Ca^{2+}-ATPase PFATP6, Na^{+}-ATPase pfATP4, H^{+}-ATPase pf^{CRT} and the ecto-nucleoside triphosphate diphosphohydrolases (NTPDases).[109] They coordinately target ATP/$ERK_{1/2}$-P2X7- NLRP3-HMGBI axis to enhance follicular helper cell immune function that may be impaired by P2X7 activation;[110] They thus decrease parasite invasion of RBCs, malaria parasitaemia and HMGBI-mediated insulin resistance.[111,112] P2 purinergic receptors regulate insulin release while hyperglycaemia-induced renal P2X7 receptor activation enhances renal monocyte accrual via MCP-I which may result in diabetic glomerulosclerosis.[113]

In the present study, MEALD combination administration most significantly prevented malaria recrudescence/reinfection than metformin alone or placebo. It also attenuated/prevented rise in blood glucose levels, infections and other metabolic syndrome-associated risk factors with consequent improved quality of life.[114,115,116]

Artemisinins are pro-oxidants, and anti-oxidants (ROS scavengers) may interfere with their mechanism of action.[117,118] but metformin-esomeprazole-artesunate combination may offset this potential side-effect because the non-endoperoxides and probably mitohormetics, metformin and esomeprazole, may also be associated with early increases in ROS production.[119,120]

Aging and glucose loading reduce bone remodelling and decrease osteoblast-derived osteocalcin which enhances insulin sensitivity in adipocytes.[121] Also, plasmodial products such as the metabolite haemozoin, a biocrystalline haemoglobin degradation material, persist in the bone marrow and promote chronic bone loss through receptor activator of NF-kappaB ligand (RANKL).[122] While low doses of esomeprazole may not pose risk for osteoclastic activity as opposed to high doses, artesunate and metformin inhibit RANKL and may additively prevent bone resorption,[123,124,125] implicating their combined beneficial role in age-associated osteoporotic bone pains.[126] PPIs, which inhibit vacuolar H^{+}-ATPase, attenuate pathological hyperactivation of osteoclasts and may reduce osteolytic bone secondaries. They may decrease RANKL/ osteoprotegerin ratio,[127] inhibit osteoclast-precursor

cells and osteoclastogenesis while enhancing osteoblast cell viability at low doses.[128,129] This mechanism may also help explain present results. Blockade of RANKL signalling is also now known to improve hepatic insulin resistance and prevent development of diabetes mellitus.[130]

CONCLUSION

Owing to the present non-availability of suitable vaccines against malaria and type 2 diabetes, the only reliable bulwark against the co-morbid diseases and their complications may be the advent of a suitable preventive strategy such as a combination pill or poly-pill. Malaria and the metabolic syndrome pose overlapping aetiopathogenic mechanisms at the molecular level. Present results indicate that low doses of metformin, artesunate and esomeprazole are veritable non-toxic combination agents that may be useful for the prevention of malaria and factors of the metabolic syndrome.

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