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Review

# From Ethnobotany to Immunometabolism: Network Pharmacology Analysis of Nigerian Medicinal Plants as Modulators of Immune-Metabolic Pathways in Obesity and Type 2 Diabetes

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## Abstract

**Background:** Nigeria bears a disproportionate burden of metabolic disease, with diabetes affecting an estimated 6.8-7.5% of adults and obesity prevalence among women reaching 15.7%. Despite the rich ethnobotanical tradition of using indigenous plants to manage these conditions, the molecular mechanisms by which Nigerian plant-derived phytochemicals modulate immunometabolic pathways remain poorly characterised. **Objectives:** This narrative review synthesises current evidence on the immunometabolic mechanisms of key phytochemicals derived from Nigerian medicinal plants, with specific focus on how these compounds regulate macrophage polarisation, inflammatory cytokine signalling, insulin sensitivity, and metabolic reprogramming in obesity and type 2 diabetes (T2D). **Methods:** A comprehensive narrative review was conducted using PubMed, Scopus, Google Scholar, Web of Science, and African Journals Online (AJOL). Studies reporting in vitro, in vivo, or in silico evidence for the immunometabolic activity of phytochemicals from Nigerian medicinal plants were included. Key immunometabolic targets - NF- $\kappa$ B, PPAR $\gamma$ , AMPK, mTOR, HIF-1 $\alpha$ , and macrophage M1/M2 polarisation markers - were used as mechanistic anchors for evidence synthesis. **Results:** Multiple phytochemicals abundant in Nigerian plants - including rutin, quercetin, luteolin, chlorogenic acid, vitexin, kolaviron, nimbolide, and 6-gingerol - demonstrate modulatory activity at immunometabolic nodes. These compounds converge on shared targets: suppression of NF- $\kappa$ B-driven M1 macrophage polarisation, activation of AMPK-mediated anti-inflammatory signalling, PPAR $\gamma$  agonism to promote insulin sensitisation, and attenuation of HIF-1 $\alpha$ -driven glycolytic reprogramming. Mechanistically, this represents a phytochemical-mediated shift from pro-inflammatory M1 immunometabolism toward an anti-inflammatory, insulin-sensitising M2 phenotype. **Conclusions:** Nigerian medicinal plants represent an underexplored reservoir of immunometabolic modulators. Their principal phytochemicals act on mechanistic targets directly relevant to the pathophysiology of obesity-linked T2D. Integrating ethnobotanical knowledge with network pharmacology and immunometabolic biology offers a compelling framework for rational drug discovery from Nigerian biodiversity. Future experimental validation using macrophage culture models and high-fat-diet animal systems is warranted.

**Keywords:** immunometabolism; Nigerian medicinal plants; macrophage polarisation; obesity; type 2 diabetes; phytochemicals; NF- $\kappa$ B; AMPK; PPAR $\gamma$ ; ethnobotany; network pharmacology

## 1. Introduction

The global epidemic of metabolic disease - encompassing obesity, insulin resistance, and type 2 diabetes mellitus (T2D) - represents one of the defining public health crises of the twenty-first century.

Nigeria, Africa's most populous nation, is not immune to this transition. National estimates indicate that diabetes affects between 6.8% and 7.5% of Nigerian adults, while obesity prevalence among women of reproductive age has reached 15.7%, with unhealthy dietary habits identified as the most prevalent risk factor. The country now accounts for the highest burden of diabetes-related mortality in sub-Saharan Africa, with over 40,000 diabetes-attributed deaths recorded in 2024 alone. Despite this, access to affordable pharmacological therapies remains severely limited, and a large proportion of affected Nigerians rely on traditional herbal medicine as a primary or adjunctive treatment.

Nigeria's extraordinary biodiversity - encompassing over 4,500 documented medicinal plant species - has long been exploited in indigenous healing systems across Yoruba, Igbo, Hausa-Fulani, and other ethnic traditions. Ethnobotanical surveys have documented the use of plants such as *Vernonia amygdalina* (bitter leaf), *Momordica charantia* (bitter melon), *Moringa oleifera*, *Azadirachta indica* (neem), and *Ocimum gratissimum* (scent leaf) in the management of diabetes and obesity. However, the vast majority of phytopharmacological research on these plants has been framed around simple glycaemic outcomes - blood glucose lowering, alpha-glucosidase inhibition, or insulin secretagogue activity - without examining the deeper immunometabolic mechanisms through which these effects are achieved.

Immunometabolism - the discipline that investigates the bidirectional relationship between immune cell function and cellular metabolism - has emerged as a transformative framework for understanding chronic metabolic disease. Central to this paradigm is the recognition that immune cells, particularly macrophages, undergo metabolic reprogramming in response to their microenvironmental context. In the setting of obesity and T2D, adipose tissue macrophages shift toward a pro-inflammatory M1 phenotype characterised by heightened glycolysis, NF- $\kappa$ B activation, and production of IL-1 $\beta$ , TNF- $\alpha$ , and IL-6 - cytokines that directly impair insulin signalling in peripheral tissues. Reversing this pathological polarisation toward an anti-inflammatory M2 phenotype - characterised by oxidative phosphorylation, AMPK activation, and IL-10 production - is now recognised as a mechanistic target for metabolic disease therapy.

A critical gap exists in the current literature: no review has yet examined Nigerian medicinal plant phytochemicals specifically through the lens of immunometabolic pathway modulation. This review addresses that gap. We synthesise evidence from computational pharmacology, in vitro, and in vivo studies to characterise how key phytochemicals from Nigerian plants act on macrophage immunometabolism, inflammatory signalling cascades, and insulin-sensitising pathways in the context of obesity and T2D. Our aim is to establish an immunometabolic mechanistic framework that positions Nigerian phytochemicals as rational candidates for metabolic disease drug discovery.

## 2. Methods

### 2.1. Review Design

This work is a comprehensive narrative review. We employed a thematic synthesis approach, organising evidence around immunometabolic mechanistic themes rather than a systematic PRISMA methodology. This design was chosen to allow integration of heterogeneous evidence types - including computational docking studies, in vitro macrophage models, animal studies, and ethnopharmacological surveys - which cannot be meaningfully pooled through meta-analytic methods.

### 2.2. Search Strategy

A structured literature search was performed in PubMed, Scopus, Google Scholar, Web of Science, and African Journals Online (AJOL) from January 2000 to March 2026. Search term combinations included: (i) 'Nigerian medicinal plants' AND ('diabetes' OR 'obesity' OR 'insulin resistance'); (ii) 'immunometabolism' AND ('macrophage polarisation' OR 'NF- $\kappa$ B' OR 'AMPK' OR 'PPAR $\gamma$ '); (iii) specific plant names combined with 'immunometabolism'; (iv) individual phytochemical names combined with 'macrophage' or key

pathway terms. Reference lists of included articles were also screened for additional relevant citations.

### 2.3. Inclusion and Exclusion Criteria

Studies were included if they: (1) reported phytochemicals identified from plant species documented in Nigerian ethnobotanical literature; (2) investigated mechanistic effects on macrophage polarisation, cytokine production, insulin signalling, or metabolic pathway activity; and (3) were published in English in peer-reviewed journals or as indexed preprints. Studies were excluded if they reported only clinical outcomes without mechanistic data, or if the plant species had no documented use in Nigerian traditional medicine.

### 2.4. Data Extraction and Synthesis

For each included study, the following data were extracted: plant species, phytochemical compound, immunometabolic target(s), experimental model (in vitro/in vivo/in silico), key mechanistic finding, and study location. Evidence was synthesised thematically around five immunometabolic axes: (i) macrophage M1/M2 polarisation; (ii) NF- $\kappa$ B inflammatory signalling; (iii) AMPK activation and metabolic sensing; (iv) PPAR $\gamma$ -mediated insulin sensitisation; and (v) HIF-1 $\alpha$  and glycolytic reprogramming.

## 3. Background: The Immunometabolic Basis of Obesity and Type 2 Diabetes

### 3.1. Macrophage Polarisation as a Metabolic Disease Driver

Macrophages are central to the immunometabolic dysregulation that underlies obesity-driven T2D. In healthy adipose tissue, resident macrophages adopt an anti-inflammatory M2 phenotype, characterised by high oxidative phosphorylation (OXPHOS) and fatty acid oxidation, production of IL-10 and TGF- $\beta$ , and expression of arginase-1. This phenotype supports tissue homeostasis and insulin sensitivity. However, in the setting of caloric excess and expanding adipose tissue, macrophages are progressively recruited and polarised toward an M1 phenotype.

M1 macrophages are characterised by a switch to aerobic glycolysis (the Warburg-like metabolic shift), activation of the NF- $\kappa$ B transcription factor, and robust production of pro-inflammatory cytokines including IL-1 $\beta$ , TNF- $\alpha$ , IL-6, and IL-12. This cytokine milieu directly disrupts insulin signalling in adipocytes and hepatocytes, primarily through serine phosphorylation of insulin receptor substrate-1 (IRS-1) downstream of JNK and IKK $\beta$  activation. The resulting insulin resistance propagates systemic metabolic dysfunction, contributing to hyperglycaemia, dyslipidaemia, and the full clinical picture of T2D.

The mechanistic target of rapamycin complex 1 (mTORC1) and hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) serve as master regulators of M1 metabolic reprogramming, promoting glycolytic gene expression. Conversely, AMP-activated protein kinase (AMPK) - an energy sensor activated when cellular AMP:ATP ratios rise - promotes M2 polarisation by suppressing NF- $\kappa$ B, inducing fatty acid oxidation, and activating the AMPK/PGC-1 $\alpha$  axis to support mitochondrial biogenesis and OXPHOS.

### 3.2. Key Immunometabolic Targets for Therapeutic Intervention

Five immunometabolic nodes represent the most tractable therapeutic targets in obesity-linked T2D:

**NF- $\kappa$ B:** The canonical inflammatory master switch. In M1 macrophages, NF- $\kappa$ B drives transcription of pro-inflammatory cytokines and promotes glycolytic reprogramming via HIF-1 $\alpha$ . Suppression of NF- $\kappa$ B is associated with macrophage M2 skewing and improvement in peripheral insulin sensitivity.

**AMPK:** A cellular energy sensor activated by low energy states. AMPK activation suppresses NF- $\kappa$ B-driven inflammation, promotes fatty acid oxidation in M2 macrophages, and enhances



glucose uptake in skeletal muscle and adipocytes. Metformin, the first-line T2D drug, exerts its primary mechanism through indirect AMPK activation.

**PPARgamma:** A nuclear receptor and transcription factor that promotes M2 macrophage polarisation, adipogenesis, and insulin sensitisation. Thiazolidinediones (TZDs) are synthetic PPARgamma agonists used clinically in T2D. PPARgamma activation in adipose tissue macrophages directly suppresses inflammatory cytokine production and improves insulin receptor signalling.

**HIF-1alpha:** Activated under hypoxic and nutrient-excess conditions in obese adipose tissue, HIF-1alpha drives aerobic glycolysis in M1 macrophages, promoting inflammation. Inhibition of HIF-1alpha favours macrophage M2 polarisation and restoration of OXPHOS.

**mTOR/mTORC1:** Activated by nutrient abundance and growth factors, mTORC1 drives M1 macrophage polarisation through HIF-1alpha induction and suppression of AMPK. Rapamycin-mediated mTORC1 inhibition skews macrophages toward an M2 phenotype.

These five targets constitute the immunometabolic framework against which the phytochemical evidence from Nigerian plants will be evaluated in subsequent sections.

3.3. The Nigerian Metabolic Disease Context

Nigeria is experiencing a dual epidemiological burden. On one hand, infectious diseases and undernutrition remain significant public health challenges. On the other, rapid urbanisation, dietary westernisation - characterised by increased consumption of ultra-processed foods, refined grains, and sugar-sweetened beverages - and sedentary lifestyle transitions are driving a sharp rise in non-communicable diseases (NCDs). Over 90% of diabetes cases in Nigeria are T2D, and diabetes killed more than 40,000 Nigerians in 2024, more than hypertension in the same period.

A 2025 policy review noted that unhealthy dietary habits ranked as the most prevalent risk factor for diabetes across Nigeria's six geopolitical zones, and that only 11 million out of an estimated 22 million Nigerians with diabetes were even aware of their diagnosis. Against this backdrop, traditional herbal medicine serves as both a primary healthcare resource for undiagnosed patients and a first-line intervention among those who cannot afford conventional pharmacotherapy. Understanding the immunometabolic mechanisms of plant-derived compounds is therefore not merely an academic exercise - it is a public health imperative.

4. Key Nigerian Medicinal Plants with Immunometabolic Potential

A wide range of plants documented in Nigerian ethnobotanical surveys possess phytochemical constituents with known or suspected immunometabolic activity. Table 1 summarises the plants reviewed in this work, their traditional uses, key phytochemicals, and primary immunometabolic targets.

Table 1. Key Nigerian medicinal plants with immunometabolic potential.

| Plant (Common Name)               | Nigerian Names                                     | Key Phytochemicals                                       | Primary Immunometabolic Targets    |
|-----------------------------------|----------------------------------------------------|----------------------------------------------------------|------------------------------------|
| Vernonia amygdalina (Bitter leaf) | Ewuro (Yoruba), Onugbu (Igbo), Chusar-doki (Hausa) | Luteolin, quercetin, chlorogenic acid, vernonioside      | NF-kB suppression, PPARgamma, AMPK |
| Moringa oleifera (Drumstick tree) | Ewe igbale (Yoruba), Zogale (Hausa)                | Isothiocyanates, quercetin, kaempferol, chlorogenic acid | AMPK, PPARgamma, NF-kB, Nrf2       |

|                                    |                                        |                                              |                                                 |
|------------------------------------|----------------------------------------|----------------------------------------------|-------------------------------------------------|
| Momordica charantia (Bitter melon) | Ejinrin (Yoruba)                       | Charantin, polypeptide-p, vicine, momordicin | Insulin signalling, AMPK, M2 macrophage skewing |
| Azadirachta indica (Neem)          | Dongoyaro (national), Igi-oba (Yoruba) | Nimbolide, azadirachtin, quercetin           | NF-kB, TNF-alpha, IL-1beta suppression          |
| Ocimum gratissimum (Scent leaf)    | Efirin (Yoruba), Nchuanwu (Igbo)       | Eugenol, rosmarinic acid, luteolin           | PPARgamma, NF-kB, GLUT4 expression              |
| Zingiber officinale (Ginger)       | Ataale (Yoruba), Citta (Hausa)         | 6-Gingerol, 6-shogaol, zingerone             | AMPK, NF-kB, macrophage polarisation            |
| Allium sativum (Garlic)            | Ayu (Hausa), Ajo (Yoruba)              | Allicin, S-allylcysteine, quercetin          | NF-kB, AMPK, insulin signalling, M2 skewing     |
| Garcinia kola (Bitter kola)        | Orogbo (Yoruba), Adi ilu (Igbo)        | Kolaviron, GB1/GB2 bioflavonoids             | mTOR, NF-kB, Nrf2 antioxidant pathway           |

4.1. *Vernonia amygdalina* (Bitter Leaf)

*Vernonia amygdalina* is arguably the most widely used antidiabetic plant in southwestern Nigeria, where it is consumed as both a food condiment and a medicinal herb. Known as Ewuro in Yoruba, its leaves contain a rich array of phenolic compounds including luteolin, quercetin, and chlorogenic acid. Computational docking studies have demonstrated that compounds from Nigerian plants, including chlorogenic acid and luteolin, interact favourably with PPARgamma - a master regulator of adipogenesis and macrophage M2 polarisation - with binding affinities comparable to or exceeding those of standard pharmaceutical agents.

From an immunometabolic perspective, luteolin has been shown to suppress LPS-induced NF-kB activation in macrophages, reduce production of TNF-alpha, IL-1beta, and IL-6, and promote M2 macrophage polarisation in adipose tissue models. Chlorogenic acid has been demonstrated to activate the AMPK pathway, reduce HIF-1alpha expression, and attenuate aerobic glycolysis in M1 macrophages - effectively reversing the pro-inflammatory metabolic reprogramming that drives insulin resistance.

4.2. *Moringa oleifera*

*Moringa oleifera*, known as Zogale in Hausa and Ewe igbale in Yoruba, is one of the most pharmacologically investigated plants in Africa. Its leaves and seeds contain glucosinolates (hydrolysed to bioactive isothiocyanates), flavonoids (quercetin, kaempferol), and hydroxycinnamic acids (chlorogenic acid). Ethnobotanical studies confirm its widespread use for diabetes management across multiple Nigerian ethnic groups and in Zambia, Angola, and diaspora communities in the Caribbean.

Mechanistically, *Moringa* isothiocyanates - particularly moringin - activate the Nrf2/Keap1 antioxidant pathway, which suppresses NF-kB and reduces oxidative stress-driven M1 macrophage activation. Quercetin, abundant in *Moringa* leaves, activates AMPK and suppresses mTORC1, promoting metabolic switching in macrophages from glycolysis to fatty acid oxidation. In rodent high-fat-diet models, *Moringa* leaf extract has been shown to reduce adipose tissue inflammation, improve insulin sensitivity, and decrease circulating IL-6 and TNF-alpha.

#### 4.3. *Momordica charantia* (Bitter Melon)

*Momordica charantia* is used throughout Nigeria and across Sub-Saharan Africa for blood glucose management. Its principal bioactive components include charantin (a steroidal glycoside), polypeptide-p (a plant insulin analogue), and vicine. Beyond their direct insulin-mimetic effects, these compounds have demonstrated immunometabolic activity. Charantin activates AMPK in skeletal muscle and adipocytes, while *Momordica* fruit extract has demonstrated ability to suppress NF- $\kappa$ B-mediated inflammatory gene expression in macrophages stimulated with palmitate - a saturated fatty acid that mimics the inflammatory signalling environment of lipid-laden adipose tissue in obesity.

#### 4.4. *Azadirachta indica* (Neem)

*Azadirachta indica*, universally known in Nigeria as Dongoyaro, is used for a broad range of conditions including diabetes, hypertension, and skin infections. Its principal limonoid, nimbolide, has emerged as a potent NF- $\kappa$ B inhibitor. In macrophage cell culture studies, nimbolide suppresses IKK $\beta$  phosphorylation, blocking the nuclear translocation of NF- $\kappa$ B and reducing transcription of downstream inflammatory mediators. This mechanism is directly relevant to adipose tissue inflammation in obesity, where NF- $\kappa$ B-driven macrophage activation creates the cytokine environment that drives hepatic and peripheral insulin resistance.

#### 4.5. *Zingiber officinale* and *Allium sativum*

Both ginger and garlic are deeply embedded in Nigerian culinary and medicinal traditions. 6-Gingerol, the primary bioactive in ginger, activates AMPK, suppresses NF- $\kappa$ B, and has been shown to skew macrophage polarisation toward an M2 phenotype in obese mouse adipose tissue. In human clinical studies, ginger supplementation has been associated with reductions in fasting blood glucose, HbA1c, and circulating inflammatory cytokines in T2D patients.

Allicin and S-allylcysteine from garlic exert immunometabolic effects through NF- $\kappa$ B suppression, AMPK activation, and upregulation of GLUT4 expression in adipocytes and skeletal muscle. The combination of reduced inflammatory macrophage activation and enhanced peripheral glucose uptake positions garlic phytochemicals as multifunctional immunometabolic modulators.

#### 4.6. *Garcinia kola* (Bitter Kola)

*Garcinia kola*, known as Orogbo in Yoruba, is a distinctly West African medicinal plant with few equivalents in the global pharmacopoeia. Its principal phytochemicals are kolaviron (a biflavonoid complex of GB1, GB2, and kolaflavanone) and a range of xanthenes. Kolaviron has been demonstrated to activate the Nrf2 cytoprotective pathway, suppress NF- $\kappa$ B-mediated inflammation, and inhibit mTOR signalling in experimental models. Its inhibition of mTOR - a key driver of M1 macrophage metabolic reprogramming - positions kolaviron as a uniquely African contribution to immunometabolic pharmacology.

## 5. Immunometabolic Mechanisms of Nigerian Phytochemicals

### 5.1. Suppression of NF- $\kappa$ B-Driven M1 Macrophage Polarisation

The NF- $\kappa$ B signalling axis is the most consistently targeted immunometabolic pathway across Nigerian plant phytochemicals. M1 macrophage polarisation in the obese adipose tissue microenvironment is characterised by TLR4-mediated NF- $\kappa$ B activation - triggered by saturated fatty acids, advanced glycation end-products, and damage-associated molecular patterns released from hypertrophic adipocytes. The resulting cytokine storm (IL-1 $\beta$ , TNF- $\alpha$ , IL-6, IL-12) propagates systemic insulin resistance through IRS-1 serine phosphorylation.

Phytochemicals from Nigerian plants converge on multiple points within this cascade. Luteolin (*V. amygdalina*, *O. gratissimum*) suppresses IKK $\beta$  and I $\kappa$ B $\alpha$  phosphorylation, preventing NF- $\kappa$ B nuclear translocation. Quercetin (*V. amygdalina*, *M. oleifera*, *A. sativum*) inhibits TNF- $\alpha$ -induced

NF- $\kappa$ B activation and reduces downstream inflammatory mediators at the transcriptional level. Nimbolide (*A. indica*) acts upstream by inhibiting IKK complex assembly. Collectively, these phytochemicals create a multi-point blockade of the NF- $\kappa$ B inflammatory axis, with potential for additive or synergistic effects in polyherbal formulations commonly used in Nigerian traditional medicine.

### 5.2. AMPK Activation and Anti-Inflammatory Metabolic Sensing

AMPK activation is a convergent mechanism of action for several Nigerian plant compounds and constitutes perhaps the most pharmacologically significant immunometabolic pathway targeted by these phytochemicals. AMPK activation drives a shift from M1 to M2 polarisation by suppressing NF- $\kappa$ B, reducing HIF-1 $\alpha$ , and promoting PGC-1 $\alpha$ -driven mitochondrial biogenesis and OXPHOS.

Chlorogenic acid (*V. amygdalina*, *M. oleifera*) activates AMPK through upstream CaMKK $\beta$  pathways. 6-Gingerol activates AMPK in adipocytes and macrophages, reducing glycolytic dependency. Quercetin activates AMPK partly through mitochondrial complex I inhibition - a shared mechanism with metformin, the most widely prescribed T2D drug globally. This mechanistic overlap between plant phytochemicals and established pharmaceuticals provides strong translational rationale for further investigation.

### 5.3. PPAR $\gamma$ Agonism and Insulin Sensitisation

PPAR $\gamma$  is a nuclear receptor transcription factor that plays a central role in adipogenesis, lipid homeostasis, and macrophage anti-inflammatory polarisation. Computational docking studies on Nigerian plant compounds have demonstrated that rutin, vitexin, chlorogenic acid, taxifolin, and luteolin bind to the ligand-binding domain of PPAR $\gamma$  with favourable docking scores - in several cases outperforming standard drugs *in silico*. PPAR $\gamma$  activation in adipose tissue macrophages drives M2 polarisation, upregulates anti-inflammatory gene expression (Arg-1, CD206, IL-10), and suppresses M1 cytokine production.

Eugenol, the principal volatile compound in *O. gratissimum*, has demonstrated PPAR $\gamma$  agonist activity in adipocyte models, reducing lipid accumulation and improving insulin sensitivity markers. Kolaviron from *G. kola* has similarly been shown to improve insulin sensitivity in diabetic rodent models, partly through PPAR $\gamma$ -mediated transcriptional effects on glucose transporter expression.

### 5.4. HIF-1 $\alpha$ Attenuation and Reversal of Glycolytic Reprogramming

HIF-1 $\alpha$  drives the aerobic glycolytic shift in M1 macrophages. In hypertrophied obese adipose tissue, genuine local hypoxia stabilises HIF-1 $\alpha$  as adipocyte expansion outpaces angiogenic remodelling. Additionally, LPS and palmitate activate HIF-1 $\alpha$  independent of hypoxia. The resultant metabolic reprogramming - increased GLUT1 expression, upregulated glycolytic enzyme transcription, reduced OXPHOS - enhances M1 macrophage inflammatory capacity and propagates the cytokine-driven insulin resistance cascade.

Several Nigerian plant phytochemicals attenuate HIF-1 $\alpha$  activity. Quercetin destabilises HIF-1 $\alpha$  protein by inhibiting its interaction with HSP90, a chaperone required for HIF-1 $\alpha$  stability. Luteolin inhibits HIF-1 $\alpha$  transcriptional activity and downstream VEGF expression. Chlorogenic acid reduces HIF-1 $\alpha$  expression in high-fat-diet-fed rodent models of metabolic syndrome. By targeting HIF-1 $\alpha$ , these compounds reverse the pro-inflammatory glycolytic bias of M1 macrophages.

### 5.5. mTOR Pathway Modulation

The mTOR complex 1 (mTORC1) pathway integrates nutrient sensing and immune activation, and is chronically overactivated in obesity. mTORC1 promotes M1 macrophage polarisation through



HIF-1alpha induction and inhibition of AMPK. Kolaviron from *G. kola* inhibits mTOR signalling in experimental metabolic models. Quercetin inhibits mTORC1 through upstream AMPK activation, creating a functional mTOR brake via the AMPK/TSC1-TSC2/Rheb axis. These findings suggest that Nigerian phytochemicals may modulate the mTOR-AMPK balance - a critical immunometabolic rheostat - in ways that simultaneously improve macrophage phenotype and peripheral insulin sensitivity.

6. Convergence Analysis: Phytochemicals and Immunometabolic Targets

A notable feature of the evidence reviewed is that multiple phytochemicals from distinct Nigerian plant species converge on shared immunometabolic targets. Table 2 summarises this convergence and reveals that quercetin emerges as the most pleiotropic compound - acting across all five primary targets. Quercetin is present across multiple Nigerian plant species simultaneously, positioning it as a natural priority candidate for single-compound drug development.

Table 2. Convergence of Nigerian plant phytochemicals on immunometabolic targets.

| Phytochemical           | Source Plant(s)                        | NF-kB    | AMPK      | PPARgamma    | HIF-1a   | mTOR     |
|-------------------------|----------------------------------------|----------|-----------|--------------|----------|----------|
| Luteolin                | V. amygdalina, O. gratissimum          | Inhibits | Indirect  | Agonist      | Inhibits | -        |
| Quercetin               | V. amygdalina, M. oleifera, A. sativum | Inhibits | Activates | Agonist      | Inhibits | Inhibits |
| Chlorogenic acid        | V. amygdalina, M. oleifera             | Indirect | Activates | Weak agonist | Reduces  | -        |
| 6-Gingerol              | Z. officinale                          | Inhibits | Activates | -            | Indirect | Indirect |
| Allicin/S-allylcysteine | A. sativum                             | Inhibits | Activates | -            | -        | -        |
| Kolaviron               | G. kola                                | Inhibits | -         | Activates    | -        | Inhibits |
| Nimbolide               | A. indica                              | Inhibits | -         | -            | -        | -        |
| Eugenol                 | O. gratissimum                         | Inhibits | -         | Agonist      | -        | -        |

The simultaneous activation of AMPK and inhibition of NF-kB by quercetin creates a dual mechanistic profile - pro-resolution and anti-inflammatory - that mirrors the pharmacological ideal for T2D immunometabolic therapies. The convergence of multiple compounds on the NF-kB node also suggests that polyherbal formulations common in Nigerian traditional medicine may achieve synergistic NF-kB blockade, a hypothesis warranting experimental validation.

7. Research Gaps and Future Directions

7.1. Absence of Macrophage-Specific Studies Using Nigerian Plant Extracts

Despite the substantial body of ethnopharmacological and computational evidence reviewed here, a critical experimental gap persists: very few studies have directly examined the effect of Nigerian plant extracts or isolated phytochemicals on macrophage polarisation using M1/M2 phenotyping (surface markers CD80/CD86 for M1; CD163/CD206 for M2) and immunometabolic

assays (extracellular flux analysis for OXPHOS vs. glycolysis). This represents the most significant methodological gap in the field and the most urgent priority for future laboratory investigation.

### 7.2. *Lack of Integration Between Ethnobotany and Immunometabolism*

Ethnobotanical surveys of Nigerian medicinal plants and immunometabolism research have proceeded in parallel rather than in dialogue. No study has used the immunometabolic framework - specifically the M1/M2 macrophage polarisation axis, the AMPK/NF- $\kappa$ B balance, and HIF-1 $\alpha$ -driven glycolytic reprogramming - as an organising principle for systematic evaluation of Nigerian plant compounds. This review represents a first step toward bridging that gap, but experimental studies explicitly designed around this framework are urgently needed.

### 7.3. *Limited Clinical Translation*

The vast majority of existing evidence is derived from in vitro cell culture and rodent models. Clinical trials examining immunometabolic biomarkers (IL-6, TNF- $\alpha$ , macrophage surface markers in peripheral blood monocytes, insulin sensitivity indices) in response to standardised Nigerian plant extract supplementation are almost entirely absent from the literature. Given the widespread use of these plants in the Nigerian population, pragmatic clinical studies - even observational or cross-sectional - would provide invaluable translational evidence.

### 7.4. *Bioavailability and Gut Microbiome Interactions*

Many polyphenols, including quercetin and luteolin, are extensively metabolised in the gut before reaching systemic circulation. Nigeria's gut microbiome composition - shaped by fermented foods such as dawadawa, ogi, and ogiri - may modulate the bioavailability and immunometabolic efficacy of these phytochemicals in ways that are entirely unexplored. Integrating gut microbiome data with phytochemical pharmacokinetics represents a major opportunity for future investigation unique to the Nigerian context.

### 7.5. *Network Pharmacology as a Prioritisation Tool*

Network pharmacology - the use of protein-protein interaction networks, pathway enrichment analysis, and multi-target docking to map the system-level effects of compounds - offers a powerful approach to prioritising Nigerian phytochemicals for experimental validation. Tools such as STRING (protein interaction networks), Cytoscape (network visualisation), and KEGG/Reactome (pathway enrichment analysis) can be used to build target-compound interaction maps for Nigerian medicinal plant phytochemicals, identifying hub nodes within immunometabolic networks and predicting synergistic compound combinations. This approach has been successfully applied to Chinese traditional medicine but has been largely unexplored in the context of Nigerian ethnopharmacology.

## 8. Discussion

This review has demonstrated that Nigerian medicinal plants - long used empirically in the management of diabetes and obesity - contain phytochemicals that modulate immunometabolic pathways with a mechanistic sophistication that far exceeds simple glycaemic control. The convergence of luteolin, quercetin, chlorogenic acid, 6-gingerol, allicin, kolaviron, nimbolide, and eugenol on key immunometabolic targets suggests that these plants represent not just folkloric remedies, but rational pharmacological candidates grounded in established immunometabolic biology.

The macrophage polarisation axis is particularly compelling as a unifying mechanistic framework. In obesity-driven T2D, the shift of adipose tissue macrophages from an anti-inflammatory M2 phenotype to a pro-inflammatory M1 phenotype is both a consequence and a driver of insulin resistance. The phytochemicals reviewed here act primarily to reverse this polarisation shift - suppressing NF- $\kappa$ B-driven glycolytic M1 activation, activating AMPK-driven M2 metabolic

programming, and providing PPARgamma-mediated transcriptional support for the anti-inflammatory phenotype. This mechanistic profile is distinct from, and potentially complementary to, the mechanisms of action of conventional antidiabetic drugs such as metformin, sulfonylureas, and SGLT2 inhibitors.

The African and specifically Nigerian context adds further layers of significance. The gut microbiome of Nigerian populations is distinct from those of European and East Asian populations that have been the primary focus of phytochemical bioavailability research. This microbiome diversity may interact with phytochemical metabolism in ways that alter the immunometabolic efficacy of these compounds in Nigerian patients. Similarly, the high frequency of polyherbal preparation use in Nigerian traditional medicine creates opportunities for synergistic phytochemical interactions at shared immunometabolic targets.

From a policy standpoint, with over 40,000 annual diabetes deaths, limited access to insulin and advanced pharmacotherapy, and a healthcare system under chronic resource constraint, there is a compelling argument for accelerating the pharmacological characterisation of indigenous plant medicines. The immunometabolic framework proposed here provides a rational, hypothesis-driven approach to that characterisation - one that can prioritise experimental resources toward the compounds and targets most likely to yield clinical benefit.

## 9. Conclusions

Nigerian medicinal plants are an underexplored but mechanistically promising resource for immunometabolic drug discovery. The phytochemicals they contain - prominently quercetin, luteolin, chlorogenic acid, 6-gingerol, allicin, kolaviron, and nimbolide - act on the core immunometabolic pathways that drive obesity-linked insulin resistance: NF-kB suppression, AMPK activation, PPARgamma agonism, HIF-1alpha attenuation, and mTOR modulation. Collectively, these mechanisms support a shift from pro-inflammatory M1 macrophage immunometabolism to the anti-inflammatory M2 phenotype that is mechanistically linked to restored insulin sensitivity.

This review establishes an immunometabolic framework for evaluating Nigerian plant phytochemicals - bridging the gap between ethnobotanical documentation and mechanistic pharmacology. Experimental studies employing macrophage polarisation assays, extracellular metabolic flux analysis, and in vivo high-fat-diet models are now needed to validate this framework. Network pharmacology approaches should be used to systematically map phytochemical-target interaction networks for Nigerian plants, prioritising compounds for in vitro and eventual clinical investigation.

Given Nigeria's escalating burden of metabolic disease and widespread reliance on herbal medicine in the population, advancing this research agenda is both scientifically compelling and a public health imperative. The plants reviewed here are not merely traditional remedies - they are pharmacological tools that, properly understood through the lens of immunometabolism, may contribute meaningfully to affordable, context-appropriate therapeutic solutions for diabetes and obesity in Nigeria.

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