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Natural Products as Multi-Targeted Therapeutic Agents Against Chronic Inflammatory and Metabolic Disorders

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ABSTRACT: Chronic inflammatory and metabolic disorders—type 2 diabetes mellitus (T2DM), obesity, non-alcoholic fatty liver disease (NAFLD/MASLD), atherosclerosis and the metabolic syndrome—are no longer viewed as separate entities but as manifestations of a shared pathophysiology termed "metaflammation": a chronic, low-grade inflammatory state driven by over-nutrition that is inseparably coupled to metabolic dysregulation. Because this network is multifactorial and self-amplifying, single-target pharmacology is often insufficient, and there is growing interest in multi-targeted agents. Natural products—polyphenols, flavonoids, alkaloids, terpenoids and isothiocyanates such as berberine, curcumin, resveratrol, EGCG, quercetin, sulforaphane and silymarin—are archetypal polypharmacological molecules that simultaneously engage the master regulators sitting at the inflammation–metabolism interface: the energy sensor AMPK and the deacetylase SIRT1, the pro-inflammatory hub NF-κB and the NLRP3 inflammasome, the antioxidant transcription factor Nrf2, and the lipid-metabolic regulators PPARα/γ.

This review integrates the mechanistic and clinical evidence for this class, mapping how individual compounds coordinate anti-inflammatory, insulin-sensitising, lipid-lowering and antioxidant actions. Pooled clinical data are substantial: berberine, for example, produces statistically significant reductions in fasting glucose, HbA1c, HOMA-IR and the inflammatory markers IL-6, TNF-α and CRP across meta-analyses of randomised trials, while curcumin, resveratrol and silymarin improve distinct cardio-metabolic parameters.

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The principal barrier to translation is poor oral bioavailability, which modern nanoformulation and delivery strategies are increasingly able to overcome. The review concludes that multi-targeted natural products are rational, evidence-supported candidates for the integrated management of metaflammation, provided their pharmacokinetic limitations and the need for standardisation and definitive clinical trials are systematically addressed.

1. INTRODUCTION

The global epidemics of obesity and type 2 diabetes have brought into focus a fundamental biological insight: chronic inflammation and metabolic dysfunction are two faces of the same process. Over-nutrition and adiposity trigger a persistent, low-grade inflammatory state—"metaflammation"—that both arises from and drives metabolic derangement, linking obesity, insulin resistance, T2DM, NAFLD/MASLD, atherosclerosis and the metabolic syndrome into a single, self-reinforcing pathophysiological network. [1,2] Inflammatory cytokines such as TNF-α and IL-6 impair insulin signalling and β-cell function, while the metabolic stresses of excess lipid and glucose activate inflammatory sensors—creating the vicious cycle depicted in Figure 1. [2,3]

This network character has an important therapeutic implication. A disease driven by many interacting nodes, with extensive crosstalk and feedback, is intrinsically difficult to control by inhibiting any single target; blocking one pathway often provokes compensatory activation of others. [1,4] There is therefore a strong rationale for multi-targeted, polypharmacological agents that modulate several nodes at once in a balanced fashion—an approach for which conventional single-target drugs, and even NSAIDs and corticosteroids (whose long-term use carries substantial risk), are poorly suited. [4,5]

Natural products are the pre-eminent example of such polypharmacology. Secondary metabolites—polyphenols, flavonoids, alkaloids, terpenoids and isothiocyanates—have evolved to interact with multiple biological targets, and a large body of preclinical and clinical work shows that compounds such as berberine, curcumin, resveratrol, EGCG, quercetin, sulforaphane and silymarin simultaneously exert anti-inflammatory, insulin-sensitising, lipid-modulating and antioxidant effects. [3,5,6] This review examines that evidence through the lens of the shared molecular hubs at the inflammation–metabolism interface. We first describe the metaflammation concept and the principal natural-product classes; we then dissect the master regulators they engage—AMPK/SIRT1, NF-κB, the NLRP3 inflammasome, Nrf2 and the PPARs—and the polypharmacology this produces; we review the clinical evidence across metabolic diseases; and we close with the bioavailability barrier and the delivery strategies designed to overcome it.

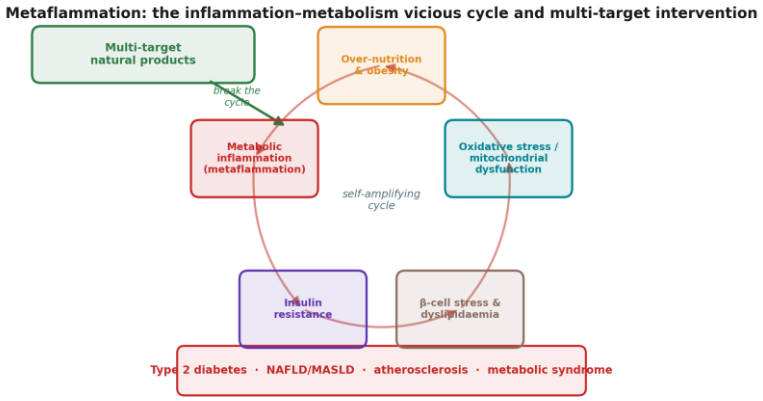

Figure 1. Metaflammation: the inflammation–metabolism vicious cycle. Over-nutrition and obesity drive chronic metabolic inflammation, which promotes insulin resistance, β-cell stress, dyslipidaemia and oxidative/mitochondrial dysfunction; these in turn amplify inflammation, closing a self-sustaining loop that culminates in type 2 diabetes, NAFLD/MASLD, atherosclerosis and the metabolic syndrome. Multi-target natural products can interrupt the cycle at several points simultaneously.

2. NATURAL PRODUCT CLASSES AND THEIR TARGETS

The natural products of interest span several chemical classes, each with characteristic pharmacology (Table 1). The isoquinoline alkaloid berberine is among the most clinically advanced; the polyphenols curcumin (a diarylheptanoid), resveratrol (a stilbene) and EGCG (a catechin), the flavonol quercetin, the flavonolignan silymarin, and the isothiocyanate sulforaphane complete the core set. What unites them is not chemistry but mechanism: each engages several of the master regulators of the inflammation–metabolism network, and it is this convergence (Section 3) that underlies their multi-target activity.

Natural product	Source	Chemical class	Principal targets	Main disorders
Berberine	*Berberis* / Coptis	Isoquinoline alkaloid	AMPK↑, NF-κB↓, NLRP3↓	T2DM, dyslipidaemia, MetS
Curcumin	*Curcuma longa*	Diarylheptanoid polyphenol	NF-κB↓, Nrf2↑, NLRP3↓	Inflammation, NAFLD, obesity
Resveratrol	Grapes, berries	Stilbene polyphenol	SIRT1↑, AMPK↑, NF-κB↓	T2DM, CVD, MetS
EGCG	Green tea	Flavan-3-ol catechin	Nrf2↑, AMPK↑, NF-κB↓	Obesity, NAFLD, atherosclerosis
Quercetin	Onion, apple, capers	Flavonol	NLRP3↓, NF-κB↓, Nrf2↑	Inflammation, T2DM
Sulforaphane	Broccoli / crucifers	Isothiocyanate	Nrf2↑, NF-κB↓	Oxidative stress, NAFLD
Silymarin	Silybum marianum	Flavonolignan	NF-κB↓, antioxidant	NAFLD, T2DM (glucose)

Table 1. Core multi-targeted natural products, their botanical sources, chemical classes, principal molecular targets and the metabolic/inflammatory disorders in which they are most studied. ↑ = activation/up-regulation; ↓ = inhibition/down-regulation.

3. SHARED MOLECULAR HUBS AT THE INFLAMMATION–METABOLISM INTERFACE

The power of these agents derives from their convergence on a small number of master regulators that couple metabolism to inflammation (Figure 2, Table 2). Understanding these hubs is the key to understanding the class.

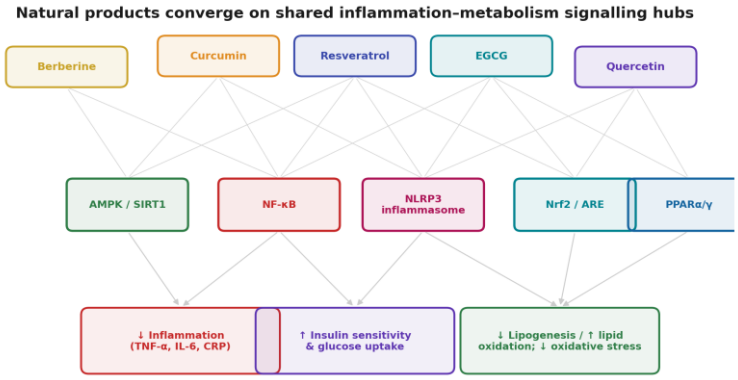

Figure 2. Natural products converge on shared inflammation–metabolism signalling hubs. Berberine, curcumin, resveratrol, EGCG and quercetin each modulate several of the master regulators—AMPK/SIRT1, NF-κB, the NLRP3 inflammasome, Nrf2/ARE and PPARα/γ—collectively reducing inflammation, improving insulin sensitivity and glucose uptake, and correcting lipid and redox imbalance.

3.1 AMPK–SIRT1: the metabolic–inflammatory coupler

AMP-activated protein kinase (AMPK) is the cell's central energy sensor, and its reduced activity is a hallmark of metabolic disease. [7,8] When activated, AMPK shifts metabolism toward catabolism—suppressing SREBP-1c-driven de novo lipogenesis, enhancing fatty-acid oxidation and GLUT4-mediated glucose uptake, and inhibiting mTOR to promote autophagy—while simultaneously restraining NF-ϰB and the associated inflammatory programme (Figure 3). [7,9] Because AMPK thus couples metabolic correction to anti-inflammatory and antioxidant defence in a single node, its activation by natural products (notably berberine, resveratrol, EGCG and curcumin) is arguably the most important single mechanism of the class; the closely linked deacetylase SIRT1 reinforces these effects. [6,7] This is the mechanistic embodiment of the metaflammation concept.

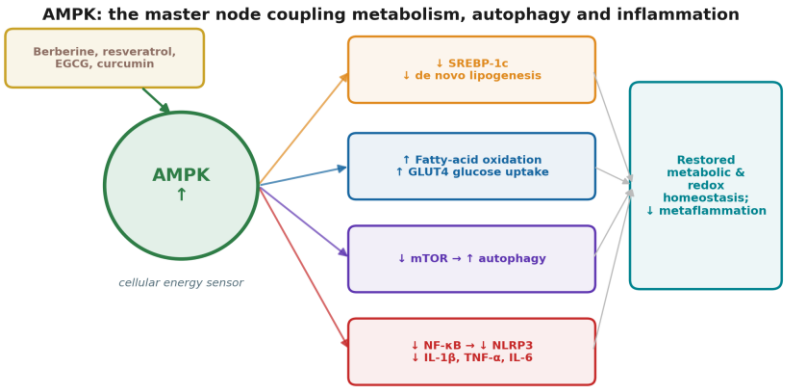

Figure 3. AMPK as the master node coupling metabolism, autophagy and inflammation. Natural-product activation of AMPK suppresses SREBP-1c-driven lipogenesis, enhances fatty-acid oxidation and glucose uptake, inhibits mTOR to promote autophagy, and down-regulates the NF-ϰB–NLRP3 axis and its cytokines—restoring metabolic and redox homeostasis and attenuating metaflammation.

3.2 NF-ϰB and the NLRP3 inflammasome

NF-ϰB is the principal transcriptional driver of inflammation, activated downstream of TLR4 and other sensors of metabolic stress, and it provides the "priming" signal for the NLRP3 inflammasome. [10,11] Persistent NLRP3 activation—triggered by mitochondrial dysfunction, oxidative stress and impaired autophagy—drives maturation of IL-1β and IL-18 and contributes directly to insulin resistance, hepatic steatosis and β-cell dysfunction. [11] Natural products attenuate this axis at multiple levels: they suppress NF-ϰB-dependent priming, limit mitochondrial ROS, stabilise lysosomes and enhance autophagy, thereby dampening NLRP3-driven metabolic inflammation. [11] This anti-inflammatory action is inseparable from the metabolic benefit.

3.3 Nrf2 and PPAR pathways

Two further hubs complete the picture. The transcription factor Nrf2 orchestrates the antioxidant response, inducing superoxide dismutase, catalase and glutathione-related enzymes to neutralise the reactive oxygen species that both cause and result from metabolic stress; sulforaphane and EGCG are especially potent Nrf2 activators. [1,12] The peroxisome-proliferator-activated receptors PPARα and PPARγ govern lipid oxidation and adipocyte function and insulin sensitivity, and several natural products act as partial PPAR modulators. [1,6] The engagement of Nrf2 and PPARs alongside AMPK and NF-ϰB is what converts these compounds from simple antioxidants into genuine metabolic–inflammatory regulators.

Molecular hub	Role at the interface	Effect of natural-product modulation
AMPK / SIRT1	Energy sensing; metabolic–inflammatory coupler	Activation → ↓lipogenesis, ↑glucose uptake, ↑autophagy, ↓inflammation
NF-ϰB	Master pro-inflammatory transcription factor	Inhibition → ↓TNF-α, IL-6, adhesion molecules; NLRP3 de-priming

Molecular hub	Role at the interface	Effect of natural-product modulation
NLRP3 inflammasome	Sterile inflammation; IL-1β/IL-18 maturation	Inhibition → ↓IL-1β; improved insulin sensitivity & β-cell function
Nrf2 / ARE	Antioxidant response	Activation → ↑SOD, catalase, GSH; ↓oxidative stress
PPARα / γ	Lipid metabolism; insulin sensitivity	Modulation → ↑fatty-acid oxidation; improved adipose function

Table 2. Master regulators at the inflammation–metabolism interface, their physiological roles and the consequences of natural-product modulation. Simultaneous engagement of several hubs is the basis of multi-target activity.

4. POLYPHARMACOLOGY: ONE MOLECULE, MANY TARGETS

The defining property of this class is that a single molecule modulates several hubs at once—the essence of polypharmacology and the reason natural products are well matched to a network disease. Figure 4 visualises this as a compound-by-target matrix: each of the leading agents acts on most of the core regulators, though with characteristic emphases—berberine and resveratrol are strong AMPK activators, curcumin a dominant NF-κB inhibitor, and sulforaphane and EGCG the most potent Nrf2 inducers. [5,6,11] This distributed action confers two advantages over single-target drugs: it addresses the multifactorial pathology more completely, and it raises the barrier to the compensatory escape that limits single-node inhibition. It also provides a rational basis for combining natural products with each other or with conventional agents to achieve additive or synergistic control—the berberine–silymarin combination, for instance, has been evaluated clinically for lipids and glucose. [13,14]

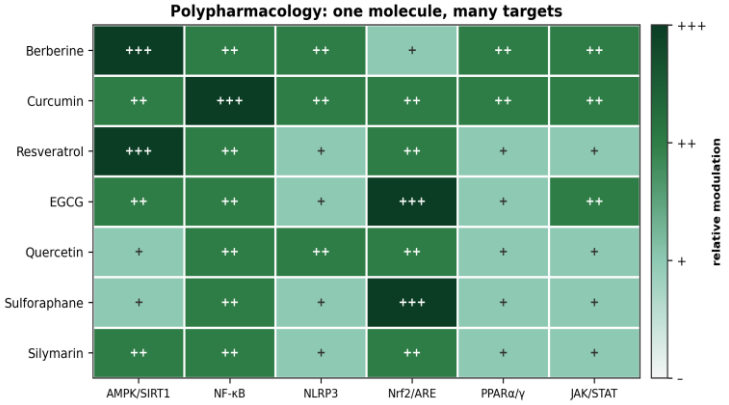

Figure 4. Polypharmacology of leading natural products, shown as relative modulation (– to +++) of six master regulators. Every compound engages multiple hubs, with characteristic emphases (e.g. berberine/resveratrol on AMPK/SIRT1; curcumin on NF-κB; sulforaphane/EGCG on Nrf2). This distributed, multi-target action matches the multifactorial nature of metaflammation.

5. CLINICAL EVIDENCE ACROSS METABOLIC DISORDERS

Crucially, the multi-target mechanisms translate into measurable clinical benefit, and the evidence base—particularly for berberine—now includes numerous randomised controlled trials and meta-analyses (Table 3). Berberine is the most compelling case: umbrella meta-analyses of RCTs report statistically significant reductions in fasting blood glucose, HbA1c, fasting insulin and HOMA-IR, together with the inflammatory markers IL-6, TNF-α and CRP, and improvements in the lipid profile (Figure 5). [15,16] This simultaneous improvement of glycaemic, inflammatory and lipid parameters in a single agent is precisely the multi-target signature predicted by its pharmacology. Network meta-analyses in T2DM further show that different phytochemicals have complementary strengths—silymarin most effective for glucose (FPG, HbA1c), resveratrol for insulin resistance and lipids, and curcumin for body-mass index—supporting individualised or combination use. [17] Across NAFLD, obesity and atherosclerosis, similar patterns of coordinated metabolic and anti-inflammatory benefit are reported. [1,7,17]

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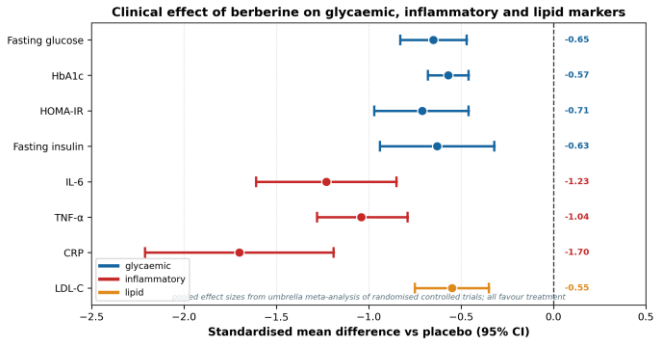

Figure 5. Clinical effect of berberine on glycaemic, inflammatory and lipid markers, expressed as pooled standardised mean differences (with 95% confidence intervals) versus placebo from meta-analyses of randomised controlled trials. All effects favour treatment, and the simultaneous improvement of glucose, inflammation and lipids illustrates the multi-target benefit. Values are compiled from the cited meta-analyses.

Natural product	Disorder	Principal clinical effects (vs placebo)	Evidence
Berberine	T2DM / MetS	↓FBG, ↓HbA1c, ↓HOMA-IR, ↓IL-6, ↓TNF-α, ↓CRP, improved lipids	Meta-analyses of RCTs [15,16]
Silymarin	T2DM	↓FPG, ↓HbA1c, ↓HOMA-IR (best glucose effect)	Network meta-analysis [17]
Resveratrol	T2DM / CVD	↓HOMA-IR, improved TC/TG/HDL/LDL, ↓BP	Network meta-analysis [17]
Curcumin	Obesity / inflammation	↓BMI, ↓CRP; anti-inflammatory	Meta-analyses / RCTs [17]
Berberine + silymarin	Dyslipidaemia / T2DM	↓lipids and ↓FPG (combination)	Meta-analysis of RCTs [14]

Table 3. Clinical evidence for multi-targeted natural products in metabolic disorders. Berberine has the strongest evidence base, with coordinated improvement of glycaemic, inflammatory and lipid parameters. FBG/FPG = fasting glucose; BP = blood pressure.

6. THE BIOAVAILABILITY BARRIER AND DELIVERY SOLUTIONS

The principal obstacle to clinical translation is pharmacokinetic. Most of the leading natural products—curcumin, resveratrol, EGCG, quercetin and berberine—have very low oral bioavailability owing to poor aqueous solubility, chemical instability, extensive first-pass metabolism and rapid elimination; curcumin's systemic bioavailability, for example, is on the order of 1% (Figure 6a). [18,19] This gap between in-vitro potency and in-vivo exposure has repeatedly limited clinical efficacy. Modern pharmaceutical science addresses it directly through a range of delivery strategies—polymeric and lipid nanoparticles, liposomes, phospholipid complexes (phytosomes), micelles and co-formulation with absorption enhancers such as piperine—which can raise bioavailability several-fold to more than an order of magnitude (Figure 6b, Table 4). [18,19,20] These approaches additionally offer sustained release and, with targeting ligands, tissue selectivity. Nanoformulation is thus not an optional refinement but a prerequisite for realising the clinical potential of this compound class.

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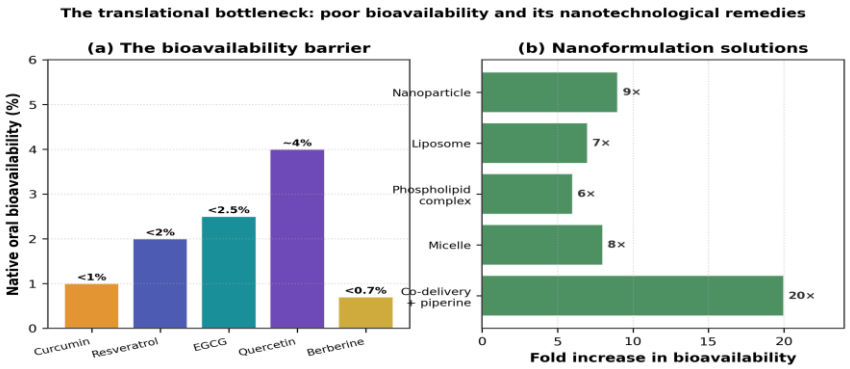

Figure 6. The translational bottleneck and its remedies. (a) Native oral bioavailability of leading natural products is very low (curcumin ~1%). (b) Representative fold increases in bioavailability achieved by nanoformulation and delivery strategies, with co-delivery plus an absorption enhancer among the most effective. Values are representative figures compiled from the cited literature.

Delivery strategy	Mechanism of enhancement	Representative benefit
Polymeric / lipid nanoparticles	Solubilisation, protection, controlled release	Several-fold ↑ exposure; tissue targeting
Liposomes	Encapsulation of hydrophobic actives	Improved stability & uptake
Phospholipid complex (phytosome)	Enhanced membrane permeation	Higher plasma levels (e.g. silymarin, curcumin)
Polymeric micelles	Solubilisation of poorly soluble actives	Improved oral absorption
Co-delivery + piperine	Inhibition of glucuronidation / efflux	Large (up to ~20-fold) ↑ curcumin bioavailability

Table 4. Delivery strategies to overcome the poor bioavailability of natural products. Combining nanoencapsulation with metabolic-enhancer co-administration is among the most effective approaches.

7. CHALLENGES AND FUTURE PERSPECTIVES

Several issues will determine the clinical future of this field. Bioavailability and formulation remain the first-order problem, and continued innovation in nanocarriers, prodrugs and structural optimisation is essential. Standardisation is a persistent concern: botanical preparations vary in composition and purity, and reproducible pharmacology requires well-characterised, standardised material and, ideally, defined single molecules with pharmaceutical-grade quality control. Clinical evidence, though strong for berberine, is heterogeneous for other agents, with variable doses, formulations and endpoints; definitive, adequately powered trials with mechanistic biomarkers of target engagement (for example circulating IL-1β, CRP or HOMA-IR) are needed. Rational combination and precision use represent a major opportunity—pairing complementary natural products, or combining them with conventional agents such as metformin to lower doses and toxicity, and using pharmacogenomic stratification (as in emerging TCF7L2-genotype berberine trials) to individualise therapy. Finally, network-pharmacology and multi-omics approaches are well suited to mapping the polypharmacology of these agents and predicting the most effective multi-target combinations before clinical testing. [4,5,15,17] The convergence of traditional multi-component wisdom with modern systems pharmacology is a particularly promising direction.

8. CONCLUSION

Chronic inflammatory and metabolic disorders share a common root in metaflammation—a self-amplifying network in which inflammation and metabolic dysfunction sustain one another. This network character makes single-target pharmacology inherently limited and creates a compelling rationale for multi-targeted therapeutics. Natural products are the archetypal solution: through coordinated modulation of the master regulators AMPK/SIRT1, NF-κB, the NLRP3 inflammasome, Nrf2

and the PPARs, agents such as berberine, curcumin, resveratrol, EGCG, quercetin, sulforaphane and silymarin simultaneously suppress inflammation, restore insulin sensitivity, correct lipid and glucose handling and reinforce antioxidant defences. This multi-target action translates into measurable clinical benefit—most robustly for berberine, which improves glycaemic, inflammatory and lipid parameters together in meta-analyses of randomised trials. Their central limitation, poor bioavailability, is increasingly tractable through nanoformulation and rational co-delivery. Realising their full promise now depends on standardised, well-characterised preparations, definitive biomarker-guided clinical trials, and the intelligent design of combinations—ideally guided by network pharmacology. Multi-targeted natural products are, on current evidence, rational and clinically credible agents for the integrated management of chronic inflammatory and metabolic disease.

Declarations

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Conflicts of interest: The authors declare no conflict of interest.

Author contributions: Conceptualisation, A.O.; investigation and writing—original draft, A.O. and A.T.; visualisation, A.T.; writing—review and editing, A.T.; supervision, A.O. All authors approved the final manuscript.

Data availability: No new primary data were generated; all data discussed are available in the cited references.

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