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Review Paper

Insulin Resistance and Metabolic Syndrome: Recognising Early Warning Signs Through an Integrative Pharmacological and Ayurvedic Perspective

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ABSTRACT

Insulin resistance (IR) is an increasingly prevalent yet underdiagnosed metabolic condition that precedes the clinical onset of type 2 diabetes mellitus (T2DM) and forms the pathophysiological core of metabolic syndrome. Recent large-scale screening data from India indicate that a substantial proportion of asymptomatic individuals already show elevated blood pressure and dysglycaemia, highlighting the silent progression of this condition at the population level. This review synthesises current literature on the molecular pathophysiology, diagnostic framework, natural history, and clinical warning signs of insulin resistance, and examines the classical Ayurvedic framework of Agni (digestive fire) and Ama (metabolic toxin accumulation) as a complementary conceptual model. Evidence for dietary, nutraceutical, pharmacological, and lifestyle interventions is critically appraised, distinguishing mechanistically well-supported approaches from those with mixed clinical evidence. Downstream complications including dyslipidaemia, hypertension, non-alcoholic fatty liver disease (NAFLD), and polycystic ovary syndrome (PCOS) are discussed, all of which share insulin resistance as a common pathophysiological thread. The review also situates these findings within the Indian public health context, drawing on nationally representative screening data, and outlines the limitations of current evidence together with directions for future research. The findings collectively indicate that insulin resistance is a reversible early-stage condition when identified through targeted screening (fasting insulin, HOMA-IR) rather than routine glucose testing alone, and that an integrated strategy combining evidence-based nutrition, physical activity, judicious pharmacotherapy, and Ayurvedic principles of digestive health may offer a practical, low-cost approach to early intervention,

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particularly relevant to resource-limited primary healthcare settings in India.

INTRODUCTION

India is currently home to more than 101 million individuals living with diabetes mellitus, according to the International Diabetes Federation (IDF) Diabetes Atlas, 11th edition[1]. Type 2 diabetes mellitus rarely develops acutely; it is typically preceded, often by several years, by a largely unrecognised metabolic disturbance — insulin resistance — that is not routinely screened for in standard clinical checkups.

Patients presenting with fatigue, weight gain, elevated blood pressure, and dyslipidaemia are frequently managed as isolated conditions by different specialists. However, a substantial body of evidence suggests that these seemingly unrelated findings often share a single underlying root cause — insulin resistance — which is not being addressed at the primary healthcare level. This fragmented approach to management is compounded by the fact that insulin resistance itself produces no distinctive symptom of its own; it manifests only through its downstream consequences, each of which is conventionally treated as a separate diagnosis.

According to the Apollo Hospitals 'Health of the Nation 2025' report, based on screening of more than 2.5 million individuals across India, 26% were found to be hypertensive and 23% diabetic, and the majority of these individuals were asymptomatic[2]. This represents a considerable population of undiagnosed at-risk individuals. Importantly, insulin resistance is reversible in its early stages, not necessarily through pharmacotherapy alone, but through appropriate dietary modification, targeted nutraceuticals, physical activity, and structured daily routines that support rather than burden metabolic function.

Within Ayurvedic medicine, this condition can be conceptually mapped to weak Agni (digestive fire) obstructed by Ama (residue of incomplete digestion). Classical Ayurvedic texts described this pattern of metabolic imbalance long before modern biochemical assays existed[3]. This review integrates a conventional pharmacological perspective with this Ayurvedic framework to provide a comprehensive, evidence-graded overview of insulin resistance, its molecular basis, warning signs, and management strategies, and situates these findings within the specific public health context of India.

The objectives of this review are threefold: first, to summarise the molecular and clinical pathophysiology of insulin resistance and its relationship to metabolic syndrome; second, to critically evaluate the evidence base for dietary, nutraceutical, Ayurvedic, pharmacological, and lifestyle interventions; and third, to examine the burden of insulin resistance-related conditions within the Indian population and the implications for primary care screening practice.

This topic carries particular relevance for undergraduate and graduate pharmacy education, since insulin resistance sits at the intersection of pharmacology, pharmacognosy, and clinical nutrition — three domains that are frequently taught separately but rarely integrated into a single clinical picture. Pharmacy professionals are often the most accessible healthcare contact for patients, particularly in Indian community pharmacy settings, and are therefore well positioned to recognise early warning signs, counsel on nutraceutical and lifestyle interventions, and refer patients for appropriate biochemical screening before overt diabetes develops. This review is written with that translational, practice-oriented purpose in mind, rather than as a purely academic exercise.

MATERIALS AND METHODS

This review is based on a narrative literature search conducted using PubMed and PubMed

Central (PMC), with additional cross-referencing of Google Scholar for recent publications. Search terms included combinations of 'insulin resistance', 'chronic low-grade inflammation and insulin resistance', 'IRS-1 PI3K Akt signalling', 'acanthosis nigricans and hyperinsulinaemia', 'metabolic syndrome diagnostic criteria', 'insulin resistance PCOS NAFLD', 'curcumin and GLUT4', 'cinnamon and glycaemic control', 'ashwagandha and cortisol', 'thiazolidinedione insulin resistance', 'ICMR-INDIAB', and 'Agni Ama Ayurveda metabolic syndrome'. Priority was given to peer-reviewed articles, systematic reviews, and meta-analyses where available, and nationally representative epidemiological data were used wherever possible to contextualise the Indian disease burden. For the Ayurvedic component, peer-reviewed Ayurvedic journal articles were preferentially cited over general health websites, in order to allow verifiability of claims.

This is not a systematic review in the strict methodological sense; no formal PRISMA-based screening with inclusion/exclusion criteria was applied. It is instead a narrative synthesis combining undergraduate pharmacology coursework with the Ayurvedic concept of Agni and Ama, supported throughout by literature evidence. Where the evidence base is strong (e.g., the exercise/GLUT4 mechanism), this is stated explicitly; where evidence is limited or conflicting (e.g., cinnamon supplementation), this is also stated transparently rather than presenting all claims with uniform certainty. Non-English language sources and unpublished/grey literature other than institutional reports (e.g., Apollo Hospitals, ICMR) were excluded.

RESULTS AND DISCUSSION

Pathophysiology of Insulin Resistance

Following carbohydrate ingestion, dietary starches are broken down into glucose, raising blood glucose levels. In response, the pancreas secretes insulin, which acts as a signalling 'key' that enables glucose transporters to move glucose from the bloodstream into cells for utilisation. In insulin resistance, target tissues — principally skeletal muscle, adipose tissue, and liver — become progressively less responsive to insulin signalling. Glucose uptake into cells is impaired despite adequate or elevated circulating insulin, and the pancreas compensates by secreting increasing amounts of insulin (hyperinsulinaemia). Over time, this compensatory mechanism places sustained stress on pancreatic beta cells, and in genetically or environmentally susceptible individuals, beta-cell function eventually declines, precipitating overt hyperglycaemia.

The physiological consequences are multifactorial: cells remain functionally 'starved' of glucose despite hyperglycaemia, contributing to persistent fatigue; chronically elevated blood glucose damages vascular endothelium, raising cardiovascular risk; unutilised glucose is diverted to hepatic lipogenesis and stored as visceral adiposity; and the liver, kidneys, and pancreas are subjected to sustained metabolic burden.

Chronic low-grade inflammation has been shown to play a central mechanistic role in this cascade[4], a finding that maps conceptually onto the Ayurvedic description of Ama. Because each downstream consequence (dyslipidaemia, hypertension, obesity, and eventual type 2 diabetes) is frequently managed by a different specialist in isolation, the shared upstream driver of insulin resistance is often left unaddressed.

Molecular Mechanisms of Insulin Signalling Dysfunction

At the cellular level, insulin action is mediated through the insulin receptor (IR)–insulin receptor substrate (IRS)–phosphatidylinositol 3-kinase

(PI3K)–protein kinase B (Akt) signalling cascade. Binding of insulin to its receptor activates receptor tyrosine kinase activity, leading to phosphorylation of IRS proteins, activation of PI3K, and downstream activation of Akt, which in turn promotes translocation of the GLUT4 glucose transporter to the cell membrane, enabling glucose uptake[5,6]. In insulin resistance, this pathway is disrupted at multiple points: serine (rather than tyrosine) phosphorylation of IRS-1 impairs its interaction with PI3K, reducing downstream signalling efficiency[5]. This serine phosphorylation is promoted by several factors relevant to this review, including circulating pro-inflammatory cytokines (e.g., TNF-α, IL-6), excess free fatty acids and their lipid intermediates (diacylglycerols and ceramides), and activation of stress-related kinase pathways such as JNK and IKKβ/NF-κB[5].

Adipose tissue plays a particularly central role in this process. Dysfunctional, hypertrophied adipocytes — as occur in visceral obesity — release increased quantities of adipokines, cytokines, and free fatty acids that impair insulin signalling in the liver, skeletal muscle, and pancreas[5]. Leptin, an adipocyte-derived hormone, illustrates this cross-talk: while leptin signalling normally supports glucose homeostasis via JAK2-mediated phosphorylation of IRS proteins, chronic hyperleptinaemia associated with obesity is linked to leptin resistance and impaired downstream insulin signalling[5]. Genetic factors also contribute; more than fifty mutations in the insulin receptor gene have been identified in association with rare, severe forms of insulin resistance, although such monogenic causes account for only a small minority of cases in the general population, with polygenic and acquired (lifestyle-related) factors predominating[6]. Understanding this molecular cascade is clinically relevant because it explains why interventions that reduce systemic inflammation (weight loss, exercise, certain nutraceuticals) and those that directly target the signalling pathway (thiazolidinediones, discussed later in this review) can each independently improve insulin sensitivity.

A further layer of complexity involves the progressive transition from compensated hyperinsulinaemia to overt beta-cell failure. In the early, compensated phase, pancreatic beta cells increase insulin output sufficiently to maintain normoglycaemia despite peripheral resistance; this phase may persist for years and corresponds to the period in which lifestyle intervention is most likely to achieve full reversal. Over time, however, sustained hypersecretion, combined with lipotoxic and glucotoxic stress on beta cells, leads to progressive beta-cell dysfunction and apoptosis, at which point insulin secretion becomes inadequate to compensate for peripheral resistance and overt hyperglycaemia emerges. This transition point represents a critical, and often irreversible, threshold, further reinforcing the clinical importance of identifying and intervening during the earlier compensated phase, when beta-cell reserve remains intact.

From Insulin Resistance to Metabolic Syndrome: Diagnostic Framework

The clustering of cardiometabolic risk factors around insulin resistance was first formally described by Reaven in 1988 under the term ‘Syndrome X’[7]. Since then, several expert bodies have proposed diagnostic criteria for metabolic syndrome, including the World Health Organization (1998), the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III, 2001), and the International Diabetes Federation (IDF, 2005)[8]. The IDF criteria require central obesity (ethnicity-specific waist circumference) as a mandatory component plus any two of: elevated triglycerides, reduced HDL-cholesterol, elevated blood pressure, or elevated fasting glucose. The NCEP-ATP III criteria instead require any three of five components

(waist circumference, triglycerides, HDL-cholesterol, blood pressure, fasting glucose) without treating central obesity as mandatory. These differing definitions can yield meaningfully different prevalence estimates in the same population, and this variability is a recognised limitation when interpreting epidemiological data on metabolic syndrome[8]. For clinical and educational purposes, however, the underlying message across all criteria is consistent: metabolic syndrome represents a cluster of interrelated abnormalities driven substantially by insulin resistance, rather than a set of unrelated diagnoses.

Table 1: Comparison of Major Diagnostic Criteria for Metabolic Syndrome

Criterion	WHO (1998)	NCEP-ATP III (2001)	IDF (2005)
Core requirement	Insulin resistance or diabetes (mandatory), plus 2 other factors	Any 3 of 5 factors (none mandatory)	Central obesity (mandatory), plus any 2 of 4 other factors
Obesity measure	Waist-hip ratio or BMI	Waist circumference	Ethnicity-specific waist circumference
Blood pressure	≥140/90 mmHg	≥130/85 mmHg	≥130/85 mmHg or treated
Fasting glucose	Insulin resistance required	≥110 mg/dL	≥100 mg/dL or diagnosed T2DM
Triglycerides	≥150 mg/dL	≥150 mg/dL	≥150 mg/dL or treated
HDL-cholesterol	<35 mg/dL (men), <39 mg/dL (women)	<40 mg/dL (men), <50 mg/dL (women)	<40 mg/dL (men), <50 mg/dL (women)

As illustrated in Table 1, the WHO criteria are unique in mandating direct evidence of insulin resistance or diabetes, whereas the NCEP-ATP III and IDF criteria rely on surrogate clinical markers. This distinction is clinically relevant: an individual may meet NCEP-ATP III or IDF criteria for metabolic syndrome based on blood pressure, lipid, and waist circumference thresholds alone, without any biochemical confirmation of insulin resistance itself. This further supports the argument made throughout this review that fasting insulin and HOMA-IR testing, although not part of any standard metabolic syndrome definition, provide mechanistically more direct information than the surrogate criteria in routine use.

Public Health Burden and Screening in India

The Indian Council of Medical Research–India Diabetes (ICMR-INDIAB) study, a nationally representative cross-sectional survey of more than 113,000 individuals across 31 states and union territories, reported an overall weighted prevalence of diabetes of 11.4%, prediabetes of 15.3%, hypertension of 35.5%, generalised obesity of 28.6%, abdominal obesity of 39.5%, and dyslipidaemia of 81.2%[9]. Notably, all of these metabolic non-communicable disease indicators except prediabetes were more frequent in urban than rural areas, and considerable inter-state variation was observed, with diabetes prevalence ranging several-fold between states of differing socioeconomic development[9]. These findings

collectively indicate that India is undergoing a substantial and geographically uneven metabolic disease transition.

From a health systems perspective, this scale of burden cannot be addressed through diabetes diagnosis alone; it necessitates earlier intervention at the insulin resistance stage. India's National Programme for Prevention and Control of Non-Communicable Diseases and the Ayushman Bharat Health and Wellness Centre network represent existing infrastructure through which population-level screening for hypertension and diabetes is being scaled up; however, routine screening protocols at these facilities remain centred on fasting glucose and blood pressure rather than insulin resistance-specific markers such as fasting insulin or HOMA-IR. Incorporating even opportunistic screening for early warning signs described in this review, particularly in individuals with a family history of diabetes, central obesity, or acanthosis nigricans, could meaningfully improve early detection at low additional cost within this existing infrastructure.

Natural History and Progression

The progression of insulin resistance to overt metabolic disease is variable between individuals but broadly follows a recognisable pattern. In the earliest years, resistance builds with minimal or no visible symptoms. Over three to five years, fatigue, weight gain, sugar cravings, and mildly elevated blood pressure typically emerge. Between five and ten years, a full metabolic syndrome phenotype often develops, frequently accompanied by multiple diagnoses and medications. Beyond ten years, serious complications such as elevated cardiovascular event risk and renal impairment may occur. Because this progression can remain clinically silent for a prolonged period, early identification substantially improves the likelihood of reversal.

Early Clinical Warning Signs and Screening Markers

The presence of three or more of the following features warrants targeted biochemical testing:

- Persistent fatigue, including tiredness despite adequate sleep, reflecting impaired cellular glucose uptake
- Afternoon sugar cravings, associated with relative intracellular glucose deficiency despite hyperglycaemia
- Central (abdominal) weight gain, reflecting hepatic conversion of unutilised glucose to visceral fat
- Difficulty concentrating (‘brain fog’)
- Acanthosis nigricans — dark, velvety hyperpigmented skin patches at the neck, axillae, or elbows — a recognised clinical marker of hyperinsulinaemia[10]
- Blood pressure above 130/80 mmHg
- Dyslipidaemia (elevated LDL-cholesterol and/or triglycerides, reduced HDL-cholesterol)
- Nocturnal urinary frequency
- Delayed wound healing
- Hair thinning or hormonal irregularities, frequently observed in association with PCOS

Recommended screening investigations include Fasting Blood Glucose (normal <100 mg/dL; prediabetic 100–125 mg/dL; diabetic ≥126 mg/dL), Fasting Insulin (normal <12 µIU/mL — not routinely ordered but clinically informative), HbA1c (normal <5.7%; diabetic ≥6.5%), and the HOMA-IR index, calculated as (Fasting Glucose × Fasting Insulin) ÷ 405, with values below 1.0 considered normal. Of these, fasting insulin and HOMA-IR are the most sensitive for detecting insulin resistance prior to the development of overt dysglycaemia, yet they remain the least frequently ordered in routine primary care.

Table 2: Recommended Biochemical Screening Panel for Insulin Resistance

Test	Normal Range	Prediabetic / At-Risk Range	Diabetic / Abnormal Range
Fasting Blood Glucose	<100 mg/dL	100–125 mg/dL	≥126 mg/dL
Fasting Insulin	<12 µIU/mL	12–25 µIU/mL	>25 µIU/mL
HbA1c	<5.7%	5.7–6.4%	≥6.5%
HOMA-IR	<1.0	1.0–2.5 (early resistance)	>2.5 (established resistance)
Fasting Triglycerides	<150 mg/dL	150–199 mg/dL	≥200 mg/dL
HDL-Cholesterol	>40 mg/dL (M), >50 mg/dL (F)	Borderline low	<40 mg/dL (M), <50 mg/dL (F)

Table 2 summarises the recommended screening panel discussed in this review. In primary care settings where fasting insulin assays may not be readily available or affordable, HbA1c combined with a lipid profile and waist circumference measurement can serve as a reasonable interim screening approach, with referral for fasting insulin/HOMA-IR testing reserved for individuals meeting three or more of the clinical warning signs described earlier in this review.

Role of Obesity and Adipose Tissue Dysfunction

Obesity, and in particular visceral adiposity, is among the strongest acquired risk factors for insulin resistance. Expanding adipose tissue in obesity becomes hypoxic and infiltrated by pro-inflammatory macrophages, shifting adipokine secretion toward a pro-inflammatory profile (increased leptin, resistin, and inflammatory cytokines; decreased adiponectin), and increasing circulating free fatty acid flux to the liver and muscle[5]. This adipose tissue dysfunction is now understood to be a primary driver linking obesity to insulin resistance, rather than excess fat mass alone; individuals with metabolically 'healthy' obesity and preserved adipose tissue function show comparatively less insulin resistance than those with visceral fat accumulation and adipose tissue inflammation, even at similar body mass index. This distinction has practical relevance for this review's emphasis on waist circumference and central obesity, rather than body weight alone, as a more clinically meaningful screening parameter.

Downstream Complications: Dyslipidaemia, Hypertension, NAFLD, and PCOS

The metabolic consequences of sustained insulin resistance extend across multiple organ systems. Hepatic conversion of excess glucose to triglycerides contributes to dyslipidaemia; renal sodium retention and vascular stress contribute to hypertension; and impaired beta-cell reserve over time culminates in type 2 diabetes mellitus. Collectively, these abnormalities increase the risk of cardiovascular disease, stroke, and chronic kidney disease. From a pharmacy practice perspective, this clustering has a practical implication: a patient presenting with a new prescription for an antihypertensive or a statin, without a documented diabetes diagnosis, may still be an appropriate candidate for insulin resistance screening, since dyslipidaemia and hypertension

frequently precede the biochemical diagnosis of diabetes by several years.

Insulin resistance is also increasingly recognised as a central pathophysiological driver of non-alcoholic fatty liver disease (NAFLD), promoting hepatic lipid accumulation, inflammation, and fibrosis[11]. In women, insulin resistance is closely linked with polycystic ovary syndrome (PCOS), a common endocrine disorder affecting an estimated 6–20% of women of reproductive age[12]. Hyperinsulinaemia in PCOS contributes to hyperandrogenism and ovulatory dysfunction, and the two conditions — PCOS and NAFLD — frequently coexist, sharing insulin resistance, obesity, and chronic low-grade inflammation as common upstream drivers[11,12]. This overlap illustrates why insulin resistance is best understood as a unifying metabolic disturbance rather than a series of isolated organ-specific conditions, and reinforces the rationale for screening young women presenting with menstrual irregularity or hirsutism for insulin resistance rather than treating reproductive symptoms in isolation.

Ayurvedic Perspective: Agni and Ama

Within Ayurveda, Agni refers not to literal fire but to the body's digestive and metabolic capacity. Strong Agni is associated with efficient digestion and stable energy metabolism, whereas weak Agni is associated with sluggish digestion, impaired metabolism, and eventual weight gain and fatigue[3]. The proposed mechanistic sequence by which weak Agni contributes to insulin resistance can be summarised in five stages: (i) weak Agni develops secondary to poor dietary habits, irregular eating patterns, chronic stress, or excess Kapha; (ii) digestion becomes incomplete; (iii) this generates Ama, a sticky residue of undigested material, conceptually analogous to inflammatory by-products or reactive metabolic intermediates in modern physiology; (iv) Ama is proposed to obstruct cellular signalling pathways; and (v) cells consequently become less responsive to insulin.

A useful conceptual analogy is that insulin functions as a traffic signal operating correctly, but if the road itself (Ama) is obstructed, glucose (traffic) still cannot move efficiently. Conventional pharmacological management largely addresses the signalling mechanism, whereas the Ayurvedic approach emphasises clearing the underlying obstruction before allowing normal metabolic flow to resume. Dosha imbalance is also implicated: Kapha imbalance is associated with sluggish metabolism and weight gain, while Pitta imbalance is associated with inflammation and hepatic stress; classical texts describe both as contributing jointly to this condition. It is worth noting that this Agni–Ama framework, while conceptually compelling and consistent with the inflammatory basis of insulin resistance described in modern literature, has not itself been subjected to controlled clinical validation as a diagnostic construct, and should be regarded as a complementary explanatory model rather than a replacement for biochemical diagnosis.

From a pedagogical standpoint, presenting the Agni–Ama model alongside the IRS-1/PI3K/Akt signalling pathway described earlier in this review offers pharmacy students a useful bridge between two knowledge systems that are typically taught in isolation. Both frameworks converge on a broadly similar conclusion — that a chronic, low-grade disruptive process (inflammatory mediators in modern physiology; Ama in Ayurveda) progressively impairs an otherwise intact signalling mechanism (the insulin receptor cascade; Agni) — even though the underlying vocabulary, historical origin, and degree of experimental validation differ substantially between the two systems. Recognising this conceptual parallel, without overstating the degree of formal equivalence between them, may help

students and practitioners communicate metabolic health concepts to patients using culturally familiar language, particularly in Indian primary care settings where Ayurvedic concepts remain widely understood even among patients who do not otherwise use Ayurvedic treatment.

Dietary and Nutraceutical Interventions

Ayurvedic tradition treats food as a therapeutic tool rather than merely a caloric input. The following dietary interventions are traditionally used to support insulin sensitivity, with corresponding modern evidence critically appraised below.

Beyond individual foods, overall dietary pattern and meal composition are increasingly recognised as independently important to insulin sensitivity, a consideration particularly relevant to the traditional Indian diet. Meals with a high proportion of refined carbohydrate consumed in isolation (for example, white rice or refined-flour products without accompanying protein, fibre, or fat) produce a sharper postprandial glucose excursion than the same carbohydrate consumed alongside dal, vegetables, and a source of healthy fat, because protein, fibre, and fat all slow gastric emptying and blunt the glycaemic response. This principle, sometimes described as 'food order' or 'meal sequencing' in contemporary nutrition literature, aligns closely with the traditional Indian thali format of combining grain, lentil, vegetable, and fat in a single meal, and offers a practical, culturally familiar counselling point that does not require patients to adopt an unfamiliar dietary pattern.

Bitter gourd (Momordica charantia, Karela) is among the most extensively studied. It contains charantin and polypeptide-p, compounds implicated in enhanced cellular glucose uptake and improved insulin sensitivity in laboratory and preliminary clinical studies, although most large-scale reviews conclude that standardised human trials remain necessary before definitive claims can be made[13]. Fenugreek (Trigonella foenum-graecum, Methi) contains 4-hydroxyisoleucine, and several clinical trials report improved glucose tolerance with regular consumption. Neem leaves are traditionally used for their bitter, Ama-clearing action, while spinach provides magnesium, a cofactor relevant to insulin signalling pathways.

Among whole grains, millet (bajra) and barley offer a comparatively lower glycaemic index and beta-glucan fibre content that slows glucose absorption, while moong dal provides easily digestible plant protein without sharply elevating postprandial glucose.

Turmeric (Curcuma longa, Haldi) has comparatively strong laboratory-level evidence: curcumin has been shown in cell and animal studies to upregulate GLUT4 transporter activity and improve insulin sensitivity in muscle tissue[14], although robust human trial data remain limited. Co-administration with black pepper (piperine) is traditionally recommended to enhance curcumin bioavailability.

Cinnamon (Cinnamomum verum, Dalchini) evidence is genuinely mixed and warrants honest appraisal, in contrast to how it is frequently presented in popular literature as a guaranteed intervention. Some meta-analyses report a modest reduction in fasting blood glucose with cinnamon supplementation[15], while other well-controlled trials report no significant effect[16]. This discrepancy likely reflects variation in cinnamon species, dose, and duration across studies. Cinnamon appears reasonably safe at typical culinary doses but should not be presented as a guaranteed therapeutic intervention.

Foods best avoided or minimised include refined white rice and maida-based products, sugar-sweetened beverages, repeatedly reheated cooking oils, processed and fried foods, excess dietary salt, and alcohol, all of which are associated with increased Ama formation and impaired digestive

efficiency within the Ayurvedic framework, and with adverse glycaemic and lipid profiles within conventional nutrition science.

Table 3: Summary of Evidence Strength for Dietary and Nutraceutical Interventions

Intervention	Proposed Mechanism	Evidence Level
Bitter gourd (Karela)	Charantin, polypeptide-p enhance glucose uptake	Preliminary / lab and small clinical studies
Fenugreek (Methi)	4-hydroxyisoleucine improves glucose tolerance	Moderate – supported by several small trials
Turmeric (Curcumin)	GLUT4 upregulation via AKT/AMPK signalling	Strong at lab/animal level; limited human data
Cinnamon (Dalchini)	Possible insulin-mimetic action	Mixed – conflicting meta-analyses and trials
Ashwagandha	Cortisol reduction, indirect metabolic benefit	Moderate – supported for stress reduction
Structured exercise	Insulin-independent GLUT4 translocation	Strong – well-established physiological mechanism

Table 3 consolidates the evidence appraisal presented throughout this section. A consistent pattern emerges: interventions with a well-characterised, insulin-independent mechanism (structured exercise, and to a lesser extent curcumin's effect on GLUT4) show the most consistent evidence, whereas interventions dependent on variable plant compound concentrations (cinnamon in particular) show the most inconsistent clinical results. This pattern is useful for patient counselling: nutraceuticals may be reasonably recommended as adjuncts, but physical activity should be emphasised as the primary, most reliably effective non-pharmacological intervention.

Ayurvedic Herbs and Supplements

Triphala is traditionally used to support digestion and gentle detoxification, with effects generally reported over four to eight weeks of regular use. Guduchi (Tinospora cordifolia), also referred to as Amrita in classical texts, is used for its anti-inflammatory and hepatoprotective properties. Shilajit is a mineral-rich substance used traditionally to support energy metabolism, although product purity varies considerably across commercially available preparations, making sourcing an important practical consideration.

Ashwagandha (Withania somnifera) is an adaptogen studied for its cortisol-lowering effect; because chronic stress is known to worsen insulin resistance, ashwagandha supplementation may confer indirect metabolic benefit through improved sleep and stress regulation[17]. Amla (Phyllanthus emblica), rich in vitamin C and antioxidants, is traditionally used to support hepatic function. It should be emphasised that these represent traditional dosing practices rather than formal clinical prescriptions, and individuals with diagnosed diabetes or those on pharmacological glucose-lowering therapy should consult their treating physician before initiating herbal supplementation, given the potential for herb–drug interactions.

Additional Ayurvedic and Nutraceutical Agents: Gymnema sylvestre and Syzygium cumini

Beyond the commonly discussed dietary agents described above, two further botanicals merit specific mention given their established place in Indian traditional and pharmacological literature. Gymnema sylvestre (Gurmar, literally 'sugar destroyer' in Hindi) contains gymnemic acids that are proposed to reduce intestinal glucose absorption, stimulate insulin secretion, and support pancreatic beta-cell regeneration in experimental models[21]. A systematic review and meta-analysis of ten clinical studies (419 participants) found that Gymnema sylvestre supplementation significantly reduced fasting blood glucose, post-prandial glucose, and HbA1c compared to baseline, although substantial heterogeneity between studies was noted, and most trials were of modest size and quality[22]. Syzygium cumini (Jamun, Java plum), particularly its seed extract containing the glucoside jambolin, has a long folk-medicinal history in Indian antidiabetic practice, and recent reviews summarising both experimental and clinical investigations report favourable associations with glycaemic, lipid, and blood pressure parameters relevant to metabolic syndrome[23]. As with the other nutraceuticals discussed in this review, these agents may reasonably be considered as adjunctive dietary measures, but should not be substituted for confirmed pharmacological therapy in patients with established diabetes without medical supervision, given the theoretical risk of additive hypoglycaemia when combined with glucose-lowering medication.

Proposed Screening Approach for Primary and Community Pharmacy Practice

Drawing on the warning signs, screening markers, and public health context discussed in this review, a practical, low-cost screening approach suitable for Indian primary care and community pharmacy settings can be outlined in three tiers. Tier one involves opportunistic risk assessment during routine pharmacy or clinic visits: enquiry about family history of diabetes, observation for central obesity or acanthosis nigricans, and a brief checklist of the early warning signs described earlier in this review. Tier two, triggered by a positive tier-one screen, involves basic biochemical testing already widely available at low cost — fasting blood glucose, HbA1c, and a lipid profile — alongside blood pressure and waist circumference measurement. Tier three, reserved for individuals with a positive tier-two screen but normal fasting glucose (i.e., those most likely to have isolated insulin resistance without overt dysglycaemia), involves referral for fasting insulin and HOMA-IR calculation. This tiered approach avoids the cost and logistical burden of universal fasting insulin testing while specifically targeting the population most likely to benefit — individuals who would otherwise be missed by glucose-based screening alone.

The South Asian 'Thin-Fat' Phenotype and Implications for Screening Thresholds

A body of comparative research has established that South Asian populations, including Indians, develop insulin resistance, type 2 diabetes, and cardiometabolic disease at a lower body mass index and younger age than White European populations, a pattern attributed to disproportionately higher visceral and hepatic fat, lower lean muscle mass, and reduced adiponectin relative to resistin, even at similar or lower BMI — a body composition pattern often termed the 'thin-fat' phenotype[24]. Comparative clamp studies have shown that South Asian men have significantly higher total and subcutaneous abdominal fat than BMI-matched Caucasian men despite similar overall body weight, translating into measurably greater insulin resistance at any

given BMI category[24]. This has direct practical relevance for the screening approach proposed in this review: standard international BMI cut-offs (25 kg/m² for overweight, 30 kg/m² for obesity) substantially underestimate metabolic risk in Indian patients, which is why waist circumference and the tiered screening approach outlined earlier in this review — rather than BMI alone — is emphasised as the more clinically meaningful parameter for Indian primary care and pharmacy screening contexts. A patient with a BMI in the 'normal' international range but an elevated waist circumference should not be reassured on body weight alone and may still warrant insulin resistance screening on the basis of central adiposity.

Physical Activity and Exercise Physiology

Among all non-pharmacological interventions discussed in this review, physical activity has the strongest mechanistic and clinical evidence base. Muscle contraction induces translocation of the GLUT4 glucose transporter to the cell surface through an insulin-independent signalling pathway[18]. This means that exercising skeletal muscle can facilitate glucose uptake from the bloodstream even in individuals with impaired insulin signalling, making physical activity arguably the single most effective non-pharmacological intervention against insulin resistance.

Recommended activity includes 20–30 minutes of daily yoga practice (e.g., Pavanmuktasana, Bhujangasana, Ardha Matsyendrasana, Uttanasana, and Malasana), 30 minutes of daily brisk walking, strength training for 20–30 minutes three times weekly to build metabolically active muscle mass, and swimming for 20–30 minutes two to three times weekly where feasible. Consistency appears more important than intensity; overtraining can paradoxically raise cortisol levels and counteract improvements in insulin sensitivity.

Sleep, Circadian Rhythm, and Insulin Resistance

An often-overlooked contributor to insulin resistance is sleep quality and circadian alignment. Laboratory studies of healthy adults subjected to short-term partial sleep restriction consistently demonstrate reduced glucose tolerance and impaired insulin sensitivity, with several large cross-sectional studies and meta-analyses reporting a U-shaped relationship between sleep duration and type 2 diabetes risk, in which both short (<6 hours) and long (>9 hours) sleep duration are associated with increased risk, and 7–8 hours considered optimal[20]. Mechanistically, sleep restriction and circadian misalignment (as seen in shift work or irregular sleep-wake schedules) disrupt central and peripheral clock gene expression in the liver and pancreas, alter cortisol and growth hormone secretion patterns, and increase sympathetic nervous system activity, collectively impairing insulin signalling[20]. This provides a direct physiological rationale for the dinacharya emphasis on a consistent early sleep and wake schedule described later in this review, situating an Ayurvedic lifestyle recommendation within an established modern evidence base.

Chronic Stress and the Hypothalamic–Pituitary–Adrenal Axis

Chronic psychological stress activates the hypothalamic–pituitary–adrenal (HPA) axis, resulting in sustained cortisol elevation. Cortisol antagonises insulin action by promoting hepatic gluconeogenesis, reducing peripheral glucose uptake, and favouring visceral fat deposition, thereby compounding the adipose tissue dysfunction discussed earlier in this review. This mechanistic link explains why stress-reduction interventions, including yoga, adequate sleep, and

adaptogenic herbs such as ashwagandha, are relevant to insulin resistance management despite not directly targeting glucose metabolism. It also underscores why a purely dietary or pharmacological approach that neglects stress and sleep is unlikely to achieve optimal outcomes, reinforcing the integrative, multi-pronged approach advocated throughout this review.

Lifestyle and Daily Routine (Dinacharya)

Ayurvedic dinacharya principles recommend a structured daily routine: waking early (5:30–7:00 AM) with warm water or lemon water followed by light movement or yoga; a light, warm breakfast by 8:00 AM; the largest meal at midday (12:00–1:00 PM), when digestive capacity is considered strongest, comprising bitter vegetables, whole grains, and lentils; an afternoon herbal tea and short walk (3:00–4:00 PM); a light dinner completed early (6:00–7:00 PM) avoiding heavy or fried foods; and warm turmeric milk with sleep by 10:00 PM, avoiding screen exposure close to bedtime. While direct clinical trial evidence for dinacharya as a discrete intervention is limited, its individual components (regular meal timing, morning activity, and adequate sleep) are independently supported by circadian and behavioural metabolic research.

Pharmacological Management: A Brief Overview

While the primary emphasis of this review is on early, non-pharmacological identification and reversal of insulin resistance, a brief overview of pharmacological options is relevant given the pharmacy focus of this article. Metformin, a biguanide, remains first-line therapy for insulin resistance and type 2 diabetes; it acts principally by reducing hepatic glucose output and has a favourable long-term safety profile, though gastrointestinal side effects are common[19]. Thiazolidinediones (pioglitazone, rosiglitazone) are the only class of agents that directly target insulin resistance itself, acting via activation of PPAR-γ receptors to improve adipocyte differentiation, reduce hepatic and peripheral triglycerides, and increase adiponectin secretion; their use has historically been limited by concerns regarding fluid retention, weight gain, and, for rosiglitazone, cardiovascular safety, although more recent data have been reassuring for pioglitazone specifically[19]. Newer agents, including GLP-1 receptor agonists and SGLT-2 inhibitors, improve glycaemic control and promote weight loss, thereby secondarily reducing insulin resistance, though they do not target the insulin-signalling pathway directly[19]. For pharmacy students and practitioners, an important counselling point is that none of these agents replace the need for dietary and lifestyle modification; pharmacological therapy is most effective as an adjunct to, rather than a substitute for, the non-pharmacological interventions discussed throughout this review.

Cost and accessibility are important practical considerations in the Indian context. Metformin remains among the most affordable oral antidiabetic agents available through government and private pharmacies, making it a realistic first-line option even in resource-limited settings. Thiazolidinediones and newer agents such as GLP-1 receptor agonists are considerably more expensive and less widely accessible outside urban centres, which reinforces the argument made throughout this review that early, low-cost, non-pharmacological intervention at the insulin-resistance stage — before pharmacotherapy becomes necessary — offers particular value in the Indian healthcare context, where out-of-pocket expenditure constitutes a substantial proportion of total health spending.

Patient Counselling Considerations for Pharmacists

Given the pharmacy-practice orientation of this review, it is worth outlining specific counselling points relevant to community and hospital pharmacists. When dispensing antihypertensive, lipid-lowering, or antidiabetic medication, pharmacists are well placed to ask brief screening questions covering the early warning signs described earlier in this review, and to refer patients showing three or more such signs for fasting insulin or HOMA-IR testing, particularly where fasting glucose is normal. When counselling patients on nutraceuticals such as bitter gourd, cinnamon, or Gymnema sylvestre, pharmacists should communicate the evidence strength honestly, distinguishing well-supported mechanisms (curcumin's GLUT4 effect, Gymnema sylvestre's glycaemic effect) from more provisional claims (cinnamon), consistent with the evidence-graded approach adopted throughout this review. Pharmacists should also proactively ask about concurrent use of Ayurvedic or herbal supplements in patients already prescribed metformin, sulfonylureas, or insulin, given the theoretical risk of additive hypoglycaemia, and should document and flag such combinations for the prescriber's awareness. Finally, because insulin resistance is asymptomatic in its earliest and most reversible stage, pharmacists may be uniquely positioned — more so than time-constrained physicians — to deliver repeated, incremental lifestyle counselling across multiple routine interactions with the same patient over time, an opportunity not fully captured within the current scope of most community pharmacy practice models in India.

Limitations of This Review

This review has several limitations that should be acknowledged. First, it is a narrative rather than a systematic review; no formal inclusion/exclusion screening or quality appraisal (e.g., PRISMA, GRADE) was applied, and selection of literature, while conducted in good faith, may be subject to selection bias. Second, much of the nutraceutical and Ayurvedic evidence discussed is derived from small clinical trials, animal studies, or in vitro work rather than large, adequately powered human randomised controlled trials, and this is explicitly flagged wherever relevant in the text. Third, the Agni–Ama conceptual framework, while a useful pedagogical bridge between traditional and modern understanding, has not been independently validated as a clinical diagnostic tool and should not be used as a substitute for biochemical testing. Fourth, the tiered screening approach proposed in this review is a synthesis derived from the authors' reading of the literature rather than a validated clinical algorithm, and would require prospective evaluation before implementation in practice. Finally, as an undergraduate-authored review, this article does not constitute original clinical or laboratory research, and its conclusions should be interpreted as an educational synthesis rather than a basis for individual clinical decision-making.

FUTURE DIRECTIONS

Future research would benefit from adequately powered, standardised randomised controlled trials evaluating individual and combined nutraceutical interventions (particularly bitter gourd, curcumin, and fenugreek) using validated insulin resistance endpoints such as HOMA-IR, rather than fasting glucose alone. Prospective cohort studies examining whether Ayurvedic dinacharya-based lifestyle programmes, delivered alongside conventional primary care, improve insulin sensitivity compared to standard lifestyle advice would help clarify the incremental value of this integrative approach. At the health-systems level, pilot studies evaluating the feasibility and cost-effectiveness of incorporating fasting insulin

or HOMA-IR testing into existing Ayushman Bharat Health and Wellness Centre screening protocols in India would directly address the primary-care detection gap identified in this review.

There is also a need for pharmacoeconomic research specific to the Indian setting, comparing the long-term cost of early insulin-resistance screening and lifestyle intervention against the downstream cost of managing established type 2 diabetes, hypertension, and cardiovascular disease. Given that insulin resistance frequently precedes overt diabetes by five to ten years, as discussed earlier in this review, even a modest improvement in early detection rates could plausibly generate substantial downstream healthcare savings; however, this hypothesis has not yet been formally tested within an Indian cost-effectiveness framework and represents a clear gap for future health-economics research involving collaboration between pharmacy, medical, and public health researchers.

SUMMARY OF KEY RECOMMENDATIONS

- Screen individuals with three or more early warning signs (fatigue, central weight gain, acanthosis nigricans, sugar cravings, elevated blood pressure) using fasting insulin and HOMA-IR rather than fasting glucose alone.
- Prioritise structured physical activity as the single most reliably effective non-pharmacological intervention, given its insulin-independent mechanism of glucose uptake.
- Use dietary and nutraceutical interventions (bitter gourd, turmeric, fenugreek, Gymnema sylvestre) as evidence-graded adjuncts, clearly distinguishing well-supported from weakly-supported claims when counselling patients.
- Address sleep quality, circadian regularity, and chronic stress as legitimate metabolic interventions, not merely general wellness advice.
- Reserve pharmacological therapy (metformin, thiazolidinediones, GLP-1 receptor agonists) as an adjunct to, not a replacement for, lifestyle intervention, with clear patient counselling on this point.
- Advise caution regarding herb–drug interactions in patients already on glucose-lowering medication before recommending Ayurvedic supplementation.
- Integrate Ayurvedic dinacharya principles (regular meal timing, morning activity, early sleep) where acceptable to the patient, given their independent support in circadian and behavioural metabolic literature.

CONCLUSION

Insulin resistance should be understood not as a disease in itself but as an early physiological signal indicating that dietary, activity, and lifestyle patterns require correction. Unlike many chronic conditions, it is genuinely reversible when identified early through targeted screening rather than routine glucose testing alone. An integrative approach that combines pharmacological understanding with the Ayurvedic framework of supporting Agni, reducing Ama accumulation, and rebuilding insulin sensitivity through diet, physical activity, judicious pharmacotherapy where indicated, and structured routine — applied together rather than in isolation — offers a practical and low-cost strategy for early intervention, particularly relevant to primary healthcare settings in India where routine insulin resistance screening remains uncommon despite the scale of the underlying disease burden.

For pharmacy graduates entering clinical, community, or industry practice, the core message of this review extends beyond insulin resistance

itself: it illustrates the value of looking beyond a single presenting complaint to the shared metabolic thread that often connects seemingly unrelated conditions in a patient's history. As India continues to navigate a substantial and unevenly distributed burden of metabolic non-communicable disease, pharmacists, alongside physicians, dietitians, and public health practitioners, have a meaningful role to play in shifting the point of intervention earlier — from managing established diabetes to recognising and reversing the insulin resistance that so often precedes it.

ETHICAL CONSIDERATIONS

This article is a narrative literature review and does not report original in vivo, in vitro, or human subject research conducted by the authors. Accordingly, no institutional ethics committee or institutional review board approval was required for its preparation. All clinical thresholds, dosages, and traditional practices discussed are drawn from previously published, peer-reviewed literature and are presented for educational purposes; they are not intended as individualised clinical advice, and the disclaimer provided at the end of this manuscript should be read in conjunction with all sections discussing dietary, herbal, or pharmacological interventions.

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CONFLICT OF INTEREST

The authors declare no conflict of interest associated with this manuscript.

DISCLAIMER

This article is intended for educational purposes only and does not constitute professional medical advice. Readers are advised to consult a qualified healthcare provider before making dietary changes, starting herbal or nutraceutical supplementation, or beginning a new exercise programme, particularly if already diagnosed with diabetes, cardiovascular disease, or any other medical condition, or if currently taking prescription medication.

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