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REVIEW ARTICLE

Regulatory Effects of Chromium Picolinate and Phytochemicals on Blood Glucose via AMPK Pathway Activation

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Abstract

The study examines the scientific work and clinical reports to emphasise the roles of *Brassica juncea* in glucose metabolism and glycogen synthesis, *Gymnema sylvestre* in insulin secretion and beta-cell regeneration and chromium picolinate in chromodulin synthesis and insulin receptor activation. Additionally, focus was placed on their combined ability to aggregate AMP-activated protein kinase (AMPK) signalling pathway, which play major role in insulin sensitivity and cellular energy homeostasis. By promoting glucose metabolism, chromium picolinate improves insulin sensitivity. By boosting insulin release and decreasing glucose absorption, *Gymnema sylvestre* helps manage diabetes. Glycogen production and enzyme activation are two ways that *Brassica juncea* aids in blood sugar management. When combined, these compounds enhance glucose absorption and decrease gluconeogenesis by activating the AMPK pathway. These synthetic and natural substances present encouraging diabetic treatment approaches. When combined with dietary changes, they can improve the effectiveness of treatment. Clarifying their mechanisms and improving their therapeutic uses should be the main goals of future studies.

Key words: AMP-activated protein kinase; *Brassica*; Chromium; Diabetes mellitus; Dyslipidaemias; *Gymnema*; Insulin; Metabolism; Picolinate; Regeneration.

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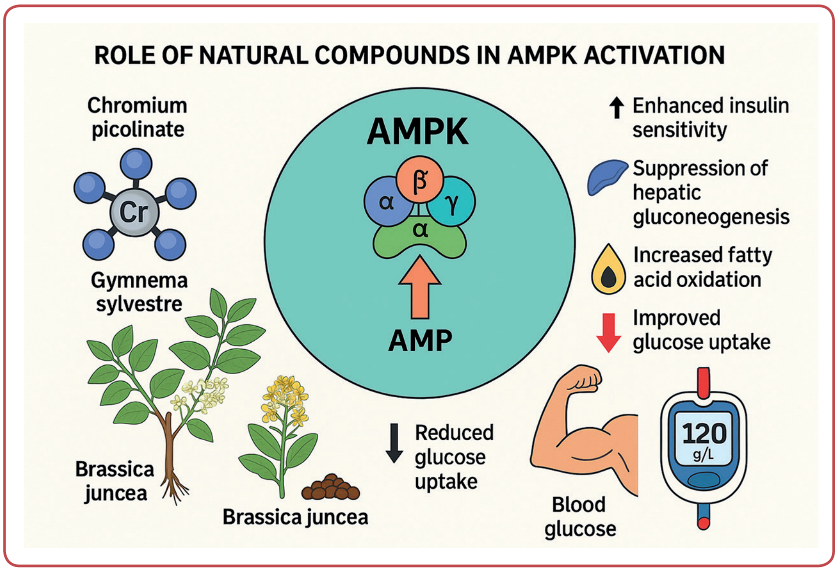

Graphical abstract

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterised by persistent hyperglycaemia, resulting from impaired insulin secretion, action, or both.[1] Insulin resistance in DM affects various metabolic tissues, notably skeletal muscle, adipose tissue and the liver, contributing to systemic metabolic dysfunction.[2] Type 2 diabetes mellitus (T2DM), formerly termed non-insulin-dependent diabetes mellitus (NIDDM), accounts for approximately 90 % of all diabetes cases worldwide. Nephropathy, cataracts and most significantly, macroangiopathy—the most common consequence among those with type 2 diabetes—are among the consequences linked to the disease.[3] Atherosclerotic plaques, which are made worse by a number of risk factors are associated to the development of macroangiopathy and cardiovascular illnesses. The seriousness of diabetes symptoms depends on the duration and type of diabetes.[4] Children with type 1 diabetes, who lack endogenous insulin, may present with symptoms such as weight loss, visual disturbances, dysuria, polydipsia and increased appetite. In contrast, individuals with early-stage T2DM may remain asymptomatic.[5] If diabetes remains untreated it can result to serval serious complications such as confusion, coma, ketoacidosis or nonketotic hyperosmolar syndrome which can lead to death if not treated well.[5] Cancer is now recognised as one of the leading causes of death among individuals with DM. In England traditional complications were accounted in more than 50 %

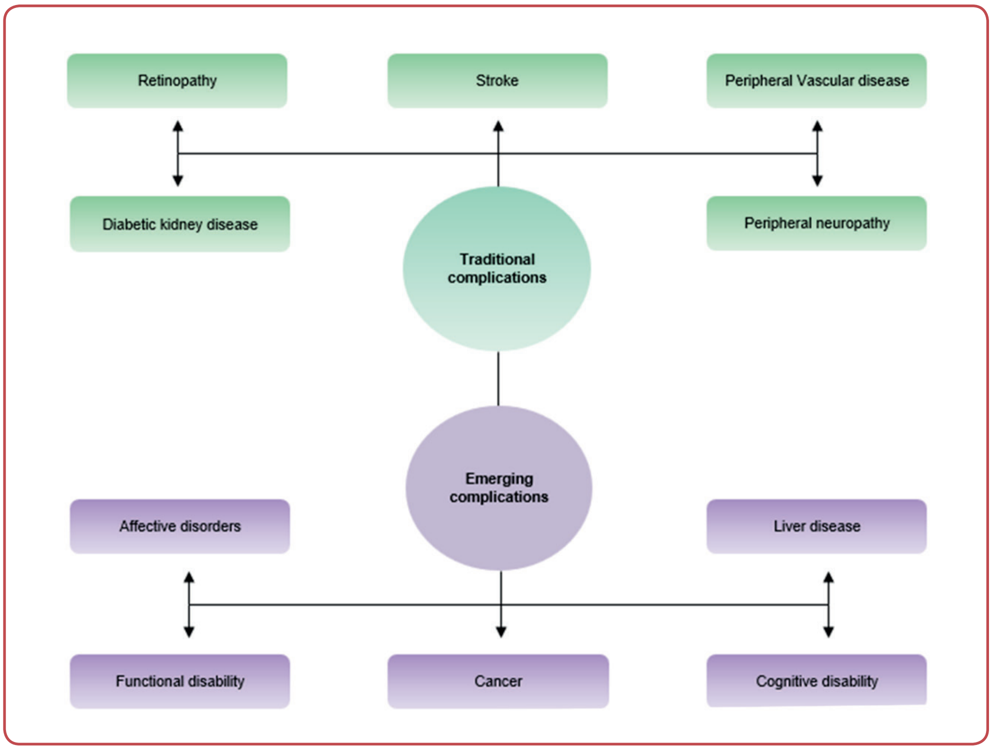

Figure 1: Traditional complications and emerging complications of diabetes mellitus

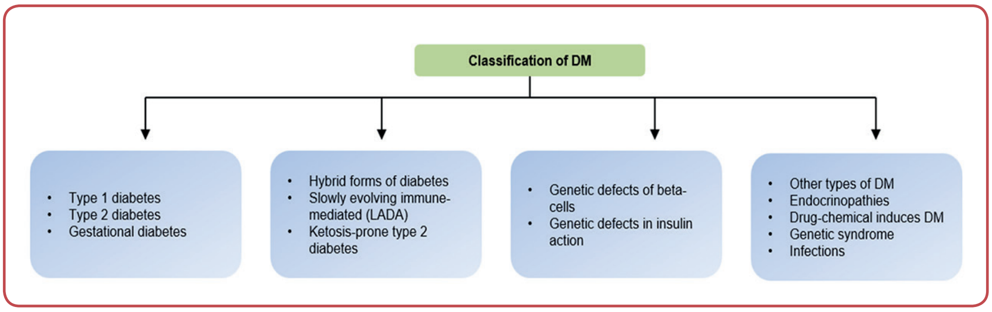

Figure 2: Classification of diabetes mellitus (DM)

of hospitalised people with DM in 2003.[6] However, by 2018, 30 % cases were reported with DM with highlighting the shift in the nature of complications over the period illustrated in Figure 1.[7]

According to WHO in 2014, 8.5 % adults aged 18 and above were diagnosed with diabetes. In 2019, 1.5 million deaths were reported with DM, 48 % among them occurred before age of 70.[8] Between 2000 and 2019, global mortality due to diabetes increased by 3 %. Notably, 460,000 deaths were attributed to diabetic kidney disease and around 20 % of cardiovascular deaths were linked to diabetes-related complications.[9] In lower-middle-income countries, the 13 % rise in mortality rate associated with diabetes has been reported. In England cancer-related diabetes increased from 22 % to 28 % from 2001 to 2018, with similar report in Australia.[10] DM is broadly classified based on its underlying pathophysiological mechanisms, which is crucial for appropriate diagnosis, management and prediction of complications (Figure 2).[11]

Classification of DM

The classification of DM has expanded beyond traditional categorisation of type 1 and type 2 diabetes to broader spectrum of aetiology (Table 1).

Several synthetic drugs are available in the market that help manage blood glucose levels and mitigate diabetes-related complications. These drugs are classified according to their mechanism of action: i. α-Glucosidases inhibitors (miglitol, acarbose, voglibose)[25] ii. Biguanides (metformin), iii. Sulfonylureas (acetohexamide, tolazamide, glipiside, glimepiride), iv. Meglitinides (repaglinide, nateglinide), v. Incretin agonists (exenatide, liraglutide), vi. DPP-4 inhibitors (sitagliptin, saxagliptin).[26, 27] These are synthetic agents used against diabetes and control glucose levels of plasma described in Figure 3.

Diabetes Control and Complication Trail (DCCT) reported that effective blood glucose control can slow down the risk of diabetes assisted complications. However, many diabetic people struggle to control the blood glucose levels with existing treatments.[28] Further, it is essential to discover some strategies to decrease the risk of diabetes and its complications. Nowadays, dietary supplements such as chromium used to manage T2DM and identify complications.[29]

Since chromium is a necessary trace mineral that improves insulin sensitivity and is needed for the metabolism of proteins, lipids and carbs, additionally, it improves glucose metabolism that has attracted a lot of attention.[30] However, dietary chromium's efficacy as a supplementary therapy is limited due to its low absorption rates.[31] As a more accessible form, chromium picolinate shows promise for those with type 2 diabetes by improving absorption and utilisation in the body. Chromium enhances insulin signalling by increasing insulin receptor sensitivity through the action of a low-molecular-weight chromium-binding substance, thereby improving glycaemic control.[32, 33]

Table 1: Classification and characteristics of diabetes mellitus

Category	Type / subtype	Description
Primary types of diabetes	Type 1 diabetes	Progressive autoimmune destruction of β-cells. Decline in insulin secretion begins ~2 years before diagnosis; rapid reduction in secretion post-diagnosis.[12, 13]
	Type 2 diabetes	Characterised by insulin resistance and inadequate compensatory insulin secretion.[14, 15]
		Pregnancy-induced hyperglycaemia. Increases risk of complications like macrosomia, preterm birth and caesarean delivery.[16, 17]
Hybrid forms of diabetes	Latent autoimmune diabetes in adults (LADA) Ketosis-prone type 2 diabetes	Autoimmune diabetes in adults; initially resembles type 2 diabetes. Gradually progresses to insulin dependence.[18] Affects primarily young African or African American individuals. Presents with ketosis but may go into remission.[19]

Genetic forms	Maturity-onset diabetes of the young (MODY) Genetic defects in insulin action	Monogenic disorder. Onset before age 25. Characterised by impaired β-cell function with preserved insulin action.[20] Mutations in insulin receptor genes. May lead to hyperinsulinemia or severe diabetes. Symptoms may include acanthosis nigricans and ovarian abnormalities.[21]
Secondary causes	Endocrinopathies	Hormonal excess from conditions like acromegaly, Cushing's syndrome, glucagonoma and pheochromocytoma can impair insulin action.[22]
	Drug- or chemical-induced diabetes Infection-induced diabetes	Certain medications or toxins can impair insulin secretion or function. Generally rare.[23] Viral infections (eg coxsackievirus B, rubella, CMV) may trigger autoimmune destruction of β-cells in genetically predisposed individuals.[24]

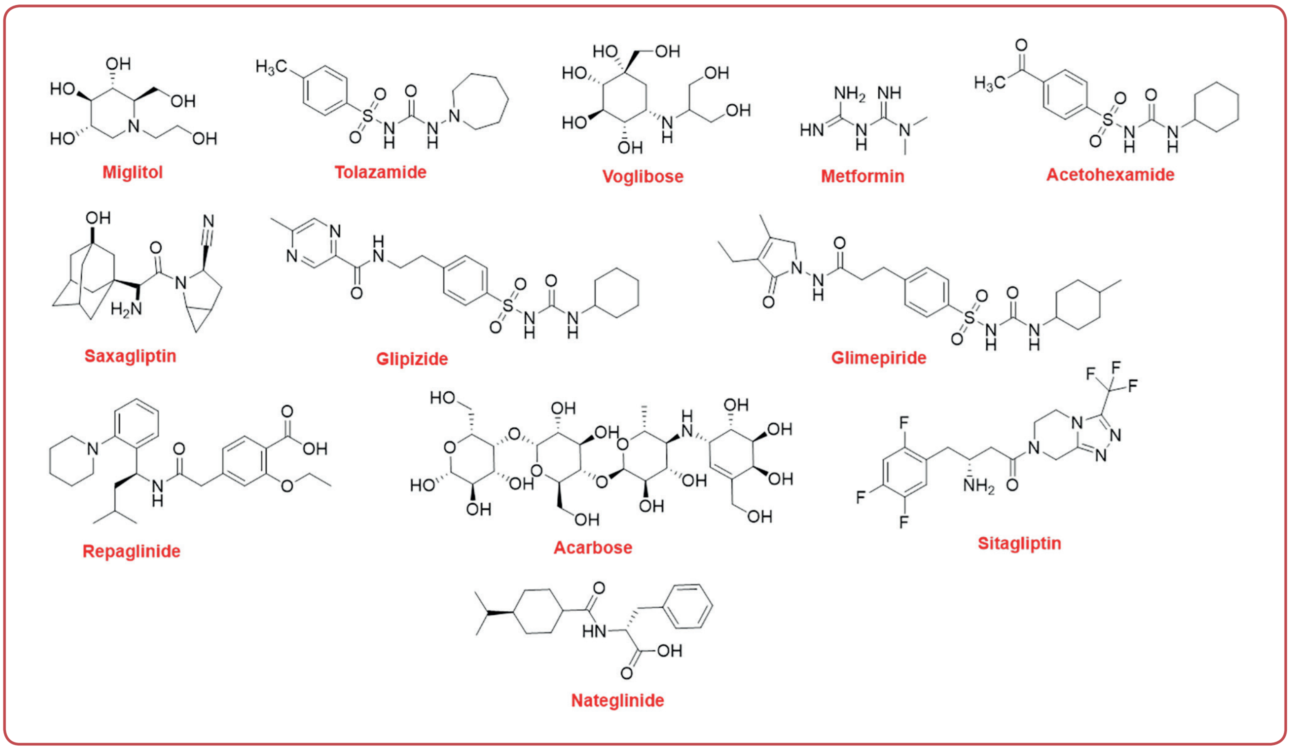

Figure 3: Marketed antidiabetic drugs

Apart from chromium, the anti-diabetic qualities of *Gymnema sylvestre*, often known as Gudmar, a traditional medicinal plant, have been acknowledged in recent years.[34] It has been demonstrated that the active ingredients in *Gymnema* (chromium picolinate acids) increases the production of insulin in pancreatic beta cells and promote their regeneration, both of these mechanisms improve blood sugar management. *Gymnema's* function in the treatment of diabetes is further supported by its capacity to prevent the intestinal absorption of glucose.[35, 36]

Another important plant is *Brassica juncea*, or mustard, which is not only an essential crop but also has medicinal uses.[37] The control of glucose metabolism is one of the many health advantages associated with its phytochemical components, especially glucosinolates.[38] By encouraging the release of enzymes that aid in the conversion of glucose into glycogen, *Brassica juncea* affects liver function and helps to maintain normal blood glucose levels.[39]

Notably, chromium picolinate, *Gymnema sylvestre* and *Brassica juncea* exert synergistic effects by activating the AMP-activated protein kinase (AMPK) pathway, a key regulator of energy balance. This results in improved glucose uptake, reduced hepatic gluconeogenesis and enhanced insulin sensitivity.[40] In people with diabetes, these substances work together to improve glucose control [41] and general metabolic health by increasing glucose absorption, decreasing gluconeogenesis and increasing insulin sensitivity.[42]

Chromium picolinate

Chromium (Cr) exists in several oxidation states, among which three are relatively stable. The Cr(II) ion is only stable in solution in the absence of oxygen.[43] The Cr(VI) ion, stable only as an oxide (eg, chromate ion, CrO_4^{2-}), is a strong oxidising agent and highly toxic. When CrO_4^{2-} enters human blood, it is rapidly reduced to Cr(III). The most biochemically relevant and stable oxidation state of chromium in solution is Cr(III), which also occurs in its principal mineral form, chromite ($FeCr_2O_4$).[44] Cr(III) complexes, such as $Cr(H_2O)_6^{3+}$, are substitutionally inert—meaning their ligands exchange very slowly with the surrounding water. This kinetic inertness is also observed in other Cr(III) complexes, including chromium picolinate ($Cr(pic)_3$), which is critical when assessing their bioavailability and metabolic functions.[45]

Chromium picolinate nutritional value

Chromium picolinate is a dietary supplement formed by chelating the essential trace mineral chromium with picolinic acid.[46] This complex improves chromium's absorption and bioavailability. It plays a vital role in metabolic functions, particularly in glucose and lipid metabolism.

Chromium has been associated with potential benefits illustrated in Figure 4, in various metabolic conditions, including impaired glucose tolerance, type 2 diabetes mellitus (T2DM), metabolic syndrome, polycystic ovary syndrome (PCOS), dyslipidaemia and weight management.[47]

Although trivalent chromium is essential for glucose metabolism, it is required only in trace amounts. A balanced diet containing fruits, vegetables, meat, fish, grains and brewer's yeast can typically meet daily chromium requirements.[49] Cases of chromium deficiency are rare. Therefore, supplementation with synthetic forms like chromium picolinate must be supported by clear biochemical evidence.[50] Additionally, trivalent chromium plays a crucial physiological role in maintaining proper lipid and carbohydrate metabolism as well as glucose and insulin homeostasis. Chromium picolinate (CrPic) is a common chemical compound used as a supplement to trivalent chromium nutrients.[50] Chromium picolinate (CrPic) is widely marketed for people with T2DM, obesity and metabolic risk.[51] However, human studies spanning over a decade indicate that CrPic supplementation does not significantly alter body composition or support weight loss in healthy individuals—even with exercise.[52]

Food source of chromium

Chromium intake and retention depend heavily on dietary composition.[58] Simple sugars increase chromium excretion, depleting reserves. Some foods categorised in Figure 5, such as dairy prod-

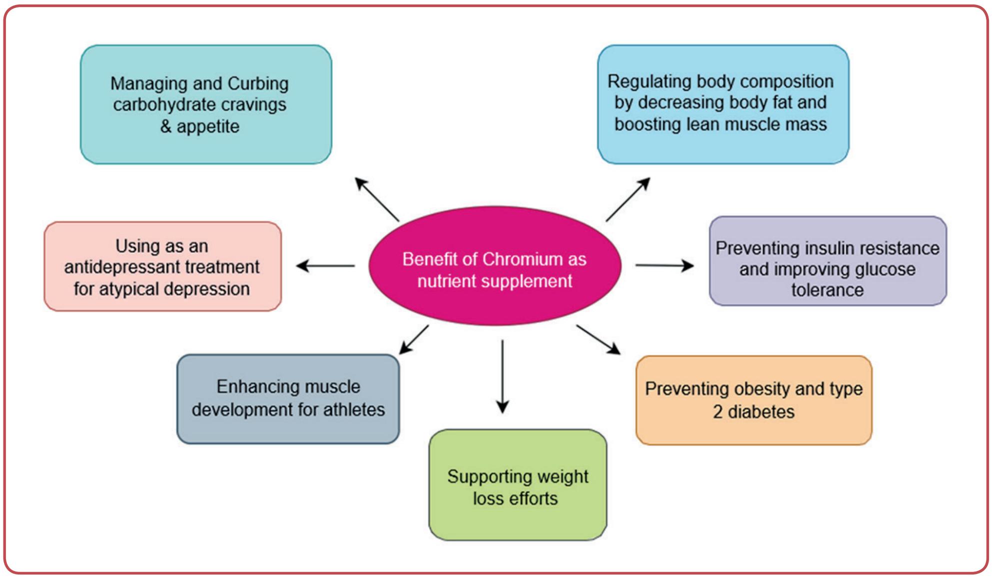

Figure 4: The benefits of chromium supplementation, including reduced carbohydrate cravings, support for healthy body composition, weight control, muscle mass promotion and improved insulin sensitivity. Chromium may also have mood-regulating effects.[45, 48]

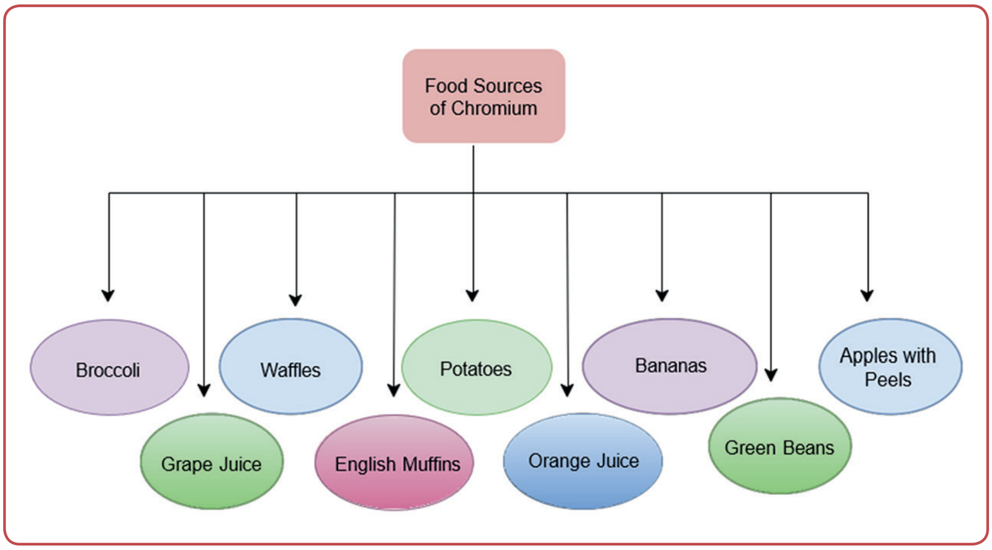

Figure 5: Fruits (bananas, apples with peels, grape juice, orange juice), vegetables (broccoli, green beans, potatoes) and grains (waffles, English muffins) are among the foods highlighted in the diagram as having chromium. Consuming these meals increases dietary chromium consumption, which is important for insulin and metabolism.

ucts, are poor sources of chromium.[59] Meats vary in their chromium content and food preparation (eg apple peeling) may reduce chromium levels significantly.[60] Fruits like bananas and apples (with peel), vegetables like broccoli and green beans and whole grains (eg English muffins) contribute meaningful chromium amounts to the diet. BBQ sauce and black pepper also contain notable levels, but their actual contribution per serving is minimal.[61]

Mechanism of chromium transportation

I. There is evidence suggesting a biochemical mechanism through which chromium enhances insulin function. The transport process of Cr(III) to insulin-responsive tissues is proposed in four key steps:[53-57]
II. The metal-binding protein transferrin carries Cr(III) ions to insulin-sensitive cells following insulin release triggered by elevated blood glucose.
III. Apo-chromodulin, a cytosolic apoprotein, binds up to four Cr(III) ions, forming the highly stable complex chromodulin.
IV. Chromodulin binds to the insulin receptor, enhancing its kinase activity and promoting phosphorylation cascades involved in glucose uptake, protein synthesis and lipid metabolism.
V. As insulin levels fall, chromodulin dissociates and is excreted in urine. The body must replenish both Cr and apo-chromodulin for sustained activity.

Impaired chromium transport is hypothesised to be linked to elevated iron levels in diabetic individuals, potentially reducing transferrin-mediated chromium delivery. Mode of action of chromium picolinate:

- Chromium IV entry: Cr(IV) enters the cell via an anion exchange channel.
- Reduction process:[62] Inside the cell, Cr(IV) reduced Cr(III).
- Binding of Cr III to apoprotein:[63] Cr(III) binds to apo-chromodulin, forming the active chromodulin complex.[64]
- Receptor activation: Chromodulin enhances insulin receptor kinase activity, promoting phosphorylation essential for glucose utilisation and insulin sensitivity.
- Release of Cr (III) and its transport:[65] Following endocytosis, the Cr(III) ion is released from the transferrin-transferrin receptor complex within the cell. It is then transported out of the endocytic vesicle through exocytosis. Once in the cytosol, Cr(III) binds to the apoprotein chromodulin, forming a highly stable chromodulin complex that facilitates insulin receptor activation.
- Effect on the insulin receptor:[66] The stable chromodulin complex enhances insulin receptor activity by promoting phosphorylation of the receptor's intracellular domains, thereby increasing its sensitivity to insulin as illustrated in Figure 6.[67]

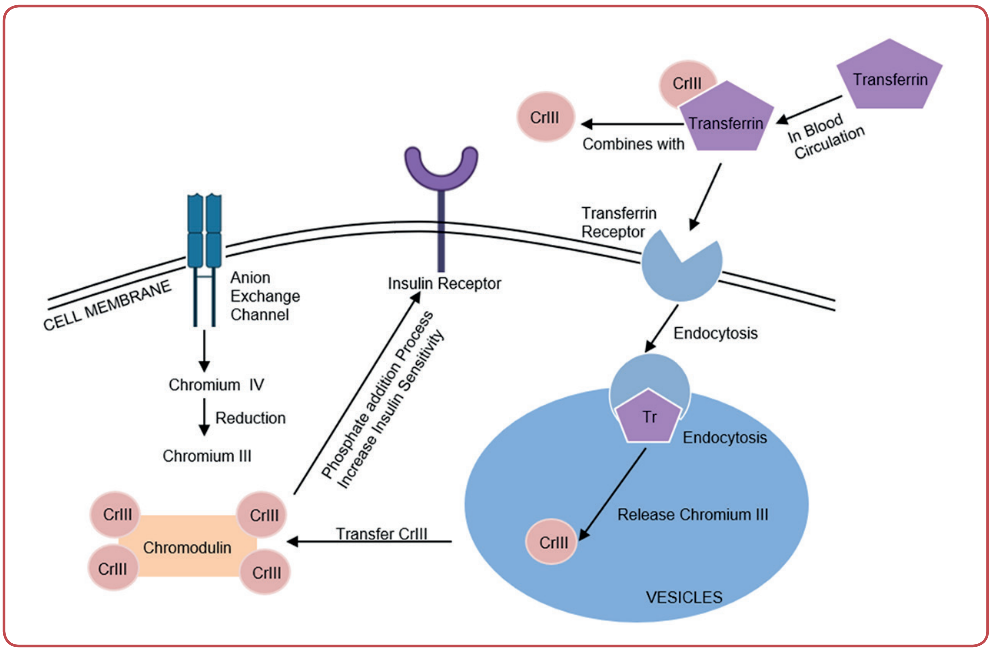

Figure 6: Absorption and metabolism of chromium (Cr). Through an anion exchange route, chromium VI enters the cell and is reduced to chromium III. Through endocytosis mediated by the transferrin receptor, chromium III can bind to transferrin in the circulation, enter the cell and then be released in vesicles. After that, it binds to chromodulin, which raises insulin sensitivity by activating the insulin receptor.

Gymnema sylvestre

Gymnema sylvestre commonly referred to as Gudmar, is a perennial, large woody climber that belonging to the *Asclepiadaceae* family, order Gentianales. The botanical classification, morphological features and synonyms are summarised in Figure 7.[68] It is widely distributed throughout India, especially in the Deccan peninsula, the Banda region, the Konkan region, the Western Ghats region and the western and northern parts of India. It is also well-known in traditional medicine for its medicinal properties.[69] The woods of Tamil Nadu, Uttar Pradesh, West Bengal, Kerala, Madhya Pradesh, Andhra Pradesh, Bihar and Chhattisgarh are home to it in India. Due to the plant's great demand in Asia, it is becoming increasingly rare and is being widely grown in southern Indian states, particularly Tamil Nadu.[70]

Gymnema leaves are said to be caustic, astringent and bitter. They temporarily impair the sense of sweetness; this remarkable quality is called "GUDMAR." Another name for it is "sugar destroyer." Gymnemic acids, gymnemagenin and gurmarin are a combination of tri-terpenes and saponins found in *Gymnema* leaves, which gives

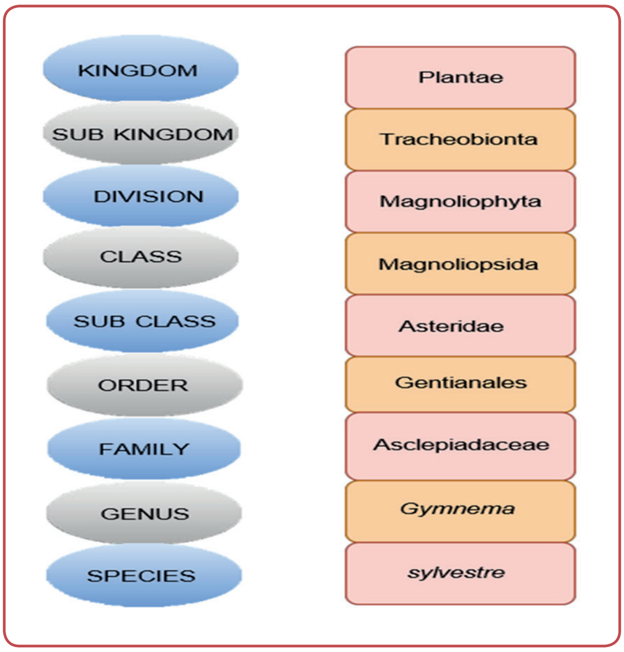

Figure 7: The taxonomic hierarchy of Gymnema sylvestre

this plant its antidiabetic qualities.[71] Additionally, its leaves are employed in anti-obesity food additives. In Ayurveda, it was traditionally used.

The plant has been overused and endangered as a result of these special characteristics.[72] It speeds up the pancreatic beta cells that secrete insulin and aids in beta cell regeneration, bringing blood sugar levels back to normal.[73] Enzymes involved in the absorption and use of glucose are activated. The main ingredient in Gudmar leaves is gymnemic acid, which stimulates the body to manufacture its own insulin by encouraging the repair or regeneration of the remaining beta cells in the islets of Langerhans, so helping to balance the excess sugar in diabetes mellitus.[74] Additionally, it stimulates the pancreas to secrete more insulin, which supports insulin production in individuals with Type 2 diabetes by converting excess glucose to glycogen. In addition to increasing the activity of the enzymes responsible for the use of glucose by insulin-dependent pathways, it prevents the intestinal absorption of glucose.[75]

Morphological characteristics and axonomical classification

Gymnema sylvestre is a large, woody, twining shrub that grows freely and climbs over tall trees.[76] The stem is firm, cylindrical, branching, especially when young. The plant bears opposite, elliptic, globous leaves range from base acute to acuminate. The leaves have a mildly astringent and bitter flavour and can temporarily suppress sweet taste perception. Some properties of *Gymnema sylvestre* given in Table 2 and phytochemical constitutents of *Gymnema sylvestre* given in Table 3.

Table 2: Characterisation of Gymnema sylvestre[77-79]

Characteristic	Details
Flowering season	April and November
Fruiting season	December- March (winter)
Chromosome number	2n = 22
Botanical synonyms	*Asclepias geminate* Roxb, *Periploca sylvestris* Retz, *Marsdenia sylvestris* (Retz)

Mechanism of action of *Gymnema sylvestre*

Gymnema sylvestre is a medicinal plant with well-documented antidiabetic properties. It exerts its primary effect on the pancreas, promoting the regeneration and proliferation of pancreatic β-cells, which are responsible for insulin secretion.[88, 89] This enhancement in β-cell mass contributes to increased insulin synthesis and release, thereby improving glycaemic control.

In addition to its pancreatic effects, *Gymnema sylvestre* also influences hepatic metabolism. It enhances the activity of liver enzymes involved in carbohydrate breakdown, supporting more efficient glucose utilisation.[90] These combined actions—stimulating insulin secretion and improving hepatic glucose metabolism—lead to a reduction in blood glucose levels, aiding in the management of diabetes mellitus.

The synergistic effect of increased insulin levels and enhanced liver enzyme activity contributes to more effective regulation of blood sugar homeostasis depicted in Figure 8.[91]

Table 3: Class of phytochemical constituents present in Gymnema sylvestre with their therapeutic uses

N	Phytochemical composition	Therapeutic uses
1	Terpenoids	Help lower blood sugar levels.[80]
2	Saponins	Antifungal, antidiabetic and hypocholesterolaemic qualities.[81]
3	Alkaloid	Hypoglycaemic activity.[82]
4	Chromium picolinate acid and its derivatives	Anti-sweet activity.[83]
5	Flavonoids	Fight infections and have antiallergic, antimicrobial, anti-inflammatory, anticancer properties.[84]
6	Gymnemasaponins (gymnemagenin and gymnestrogenin)	Hypoglycaemia in motion, ß cell
		Proliferation, gymnemagenin prevents the absorption of glucose.[85]
7	Steroids and saponins	Activate the central nervous system.[86]
8	Triterpenoid saponins	Possess anti-tumour, anti-fungal, hepatoprotective and anti-diabetic effects in numerous studies.[87]

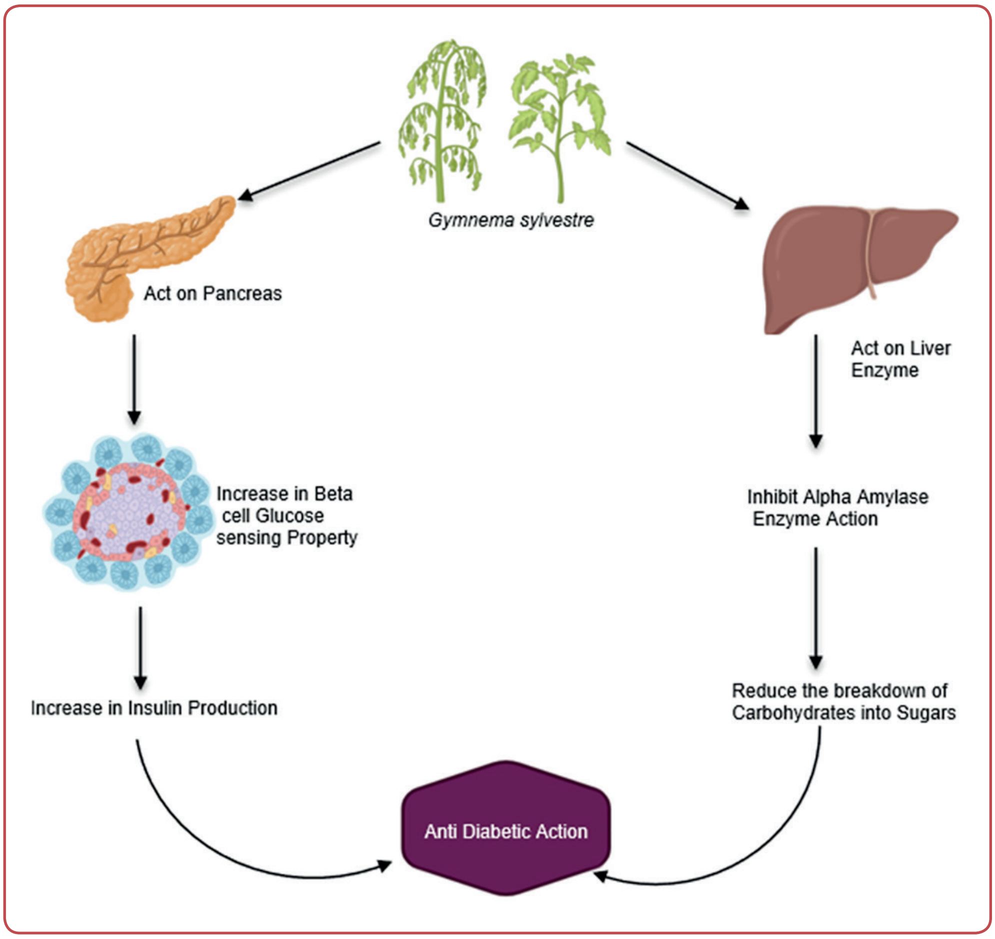

Figure 8: The anti-diabetic properties of Gymnema sylvestre. By improving beta-cell glucose sensing and raising insulin production, it operates on the pancreas. It also has an effect on liver enzymes, preventing alpha-amylase from working and decreasing the conversion of carbohydrates to sugars. Its anti-diabetic actions are a result of several processes working together.

Pharmaceutical and traditional uses

This herbal plant is useful for a variety of therapies since it has therapeutic qualities depicted in Figure 9. It has been utilised historically for therapeutic purposes and is now employed extensively in the pharmaceutical sector to produce new medications. Its medicinal properties are still being used to successfully treat a range of illnesses such as diabetes, treating corneal opacity and relieving eye discomfort are examples of corresponding traditional usage.[92, 93]

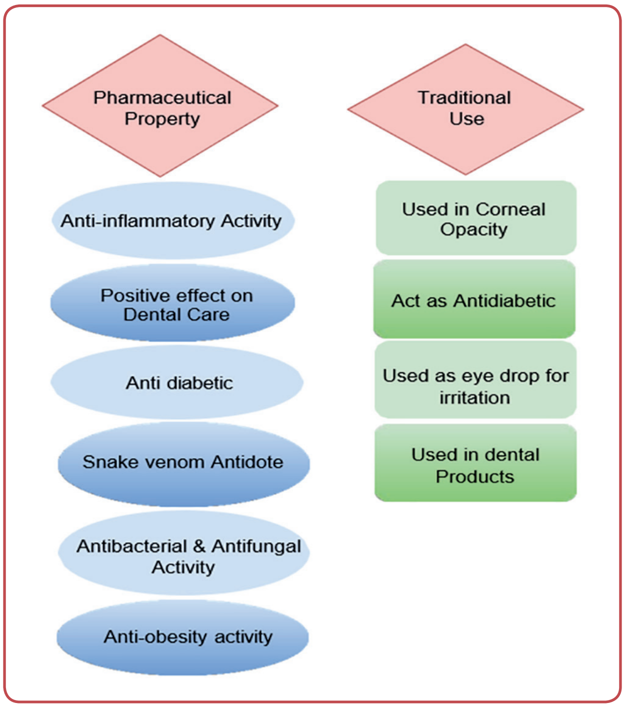

Figure 9: Medicinal substance's traditional applications with its pharmacological qualities. Properties including anti-inflammatory, antifungal, antibacterial and anti-diabetic actions are highlighted.

Brassica juncea

Brassicaceae, commonly known as the mustard plant family, is characterised by its pungent flavour due to sulphur-containing metabolites known as glucosinolates (glucoiberin, glucoraphanin, glucoerucin).[94] *Brassica* species are among the most important oilseed crops in Bangladesh, currently ranked third among all oilseed varieties.[38] They not only serve as a major source of vegetable oil but also exhibit significant therapeutic properties attributed to their diverse phytochemical composition. These include anticancer, antioxidant and anti-inflammatory effects, which make them beneficial in both traditional and modern medical practices.[95]

Among these species, *Brassica campestris* Linn—commonly known as field mustard—includes two notable varieties: Sarson and Toria. *B campestris* seeds contain around 30 % oil and show moderate sensitivity to salt.[96] Another related species, *B nigra* (black mustard), has an oil content of approximately 28 %. Both *B campestris* and *B nigra* are diploid species. In traditional systems of medicine, *B campestris* is referred to as Sarshapa and Siddhaartha in Ayurveda, Sarson in Unani, Kadugu in Tamil and Sarisha in Bangla.[97, 98]

Morphological information and taxonomical classification (leaf)

The *Brassicaceae* family exhibits a wide variety of leaf morphologies, ranging from simple to complex forms described in Figure 10.[99] It serves as a model taxon for understanding the evolutionary transition from polysymmetric to monosymmetric flowers, with its characteristic floral structure consisting of four equally sized and shaped petals.[100] The fruit types in this family are diverse, including heart-shaped, cylindrical and spherical forms. The family also presents variation in trichomes: unicellular types may be stellate, hooked, clavate, simple glandular, or Y-shaped 3–4 fids), while multicellular trichomes are typically glandular in structure.[101] Seed coloration varies across species and includes shades such as dark brown, orange-brown, lustrous brown, pale brown-black and brown.[102] Additionally, pollen grains commonly have three *colpi*, although variants with four or eight *colpi* have also been reported.

The phytochemical composition and associated therapeutic properties of *Brassica juncea* are summarised in Table 4.

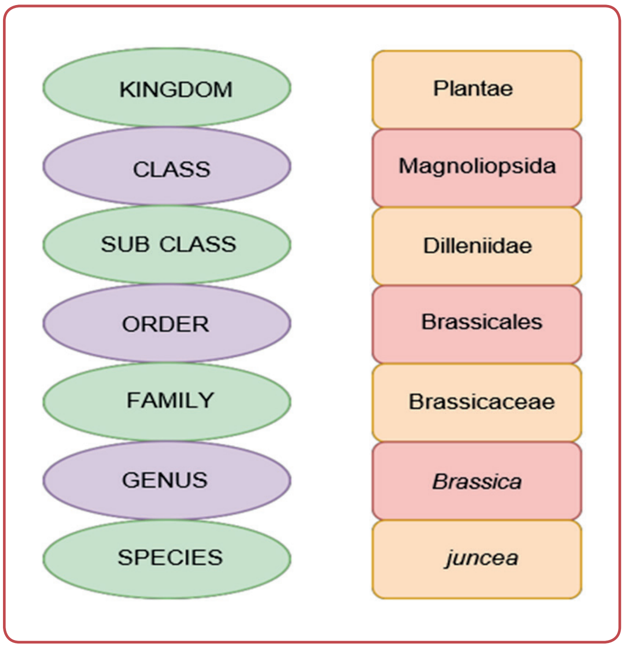

Figure 10: The taxonomic hierarchy of Brassica juncea

Table 4: Class of phytochemical constituents present in Brassica juncea with their therapeutic uses[103-106]

N	Phytochemical composition	Therapeutic uses
1	Glucosinolates	Antioxidant, detoxifier, chemo protectant, anticancer
2	Polyphenols/ flavonoids	Antioxidant, antibacterial
3	Lignin	Antioxidant, antibacterial
4	Tannin	Antibacterial
5	Carotenoids	Antioxidant
6	Palmitic, oleic and linolenic acid	Anticancer

Mode of action of *Brassica juncea*

Brassica juncea, a plant recognised for its medicinal value, significantly influences the liver, a key organ in glucose regulation.[107] Upon intake, it stimulates the secretion of enzymes involved in carbohydrate metabolism, thereby enhancing glucose utilisation and supporting blood sugar control.[108, 109] A central mechanism involves the activation of glycogen synthase, which facilitates the conversion of glucose into glycogen for storage in the liver and muscles.[110] This process helps reduce circulating glucose levels and supports glucose homeostasis, ultimately contributing to the prevention of hyperglycaemia detailed process illustrated in Figure 11.[111]

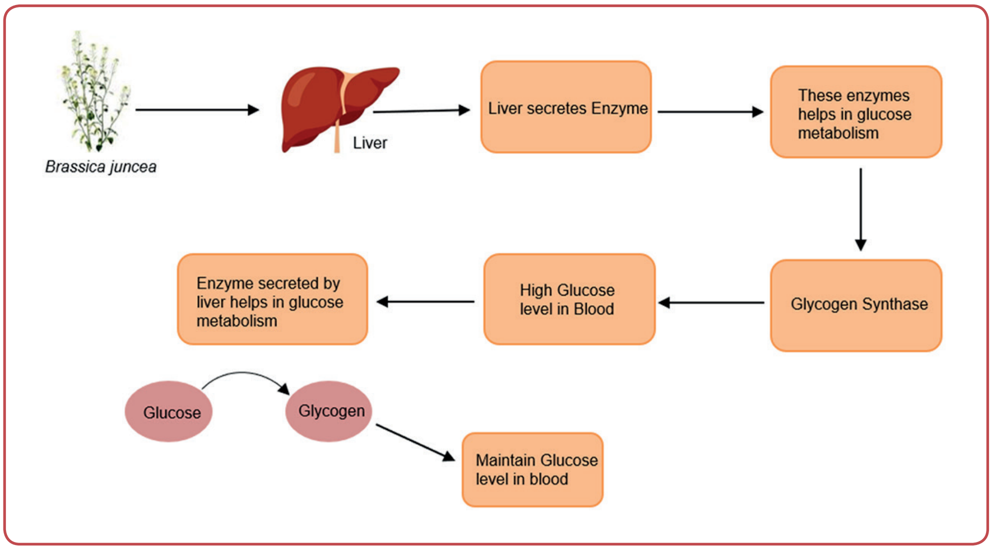

Figure 11: The anti-diabetic properties of Brassica juncea - effect on liver enzymes, eg glycogen synthetase which helps in glucose metabolism ie conversion of glucose to the glycogen; thus, maintain glucose level in blood.

Pharmaceutical properties and traditional use

Due to its wide range of therapeutic properties, this herbal plant has been traditionally used in medicine and continues to play a significant role in modern drug development. It remains a valuable resource in the pharmaceutical industry for treating various medical conditions such as antibacterial, antifungal, anti-inflammatory, anticancer, anti-diabetic, anticlastogenic and anti-obesity. Additionally, this plant has antibacterial qualities, mustard oil stimulates hair development, seeds stimulate appetite and seed juice heals sinus tumours, according to traditional applications shown in Figure 12.[112, 113]

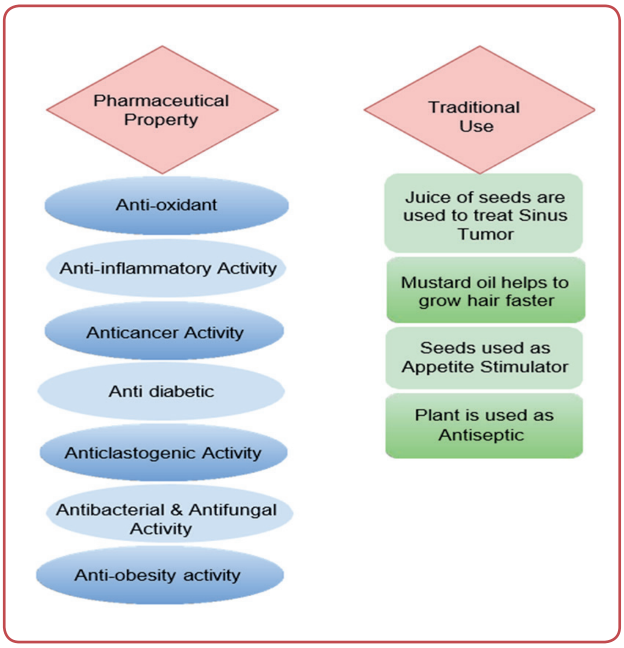

Figure 12: Plants' traditional functions and their medicinal qualities

Management of diabetes by AMPK pathway

AMPK subunits are illustrated in Figure 13.

Cellular stress conditions, such as energy deprivation, increase the AMP:ATP ratio, leading to AMP accumulation. AMP binds to the γ subunit, causing a conformational change that both activates AMPK allosterically and protects it from dephosphorylation.[42] The enzyme liver kinase B1 (LKB1 then recognises this altered structure and phosphorylates the threonine-172 (Thr172 residue on the α subunit, resulting in full activation of AMPK.[114] This leads to an increase in catalytic activity and enhanced phosphorylation of downstream targets. Consequently, catabolic pathways are upregulated, while anabolic pathways are inhibited as demonstrated in Figure 14.[115]

The rise in AMP levels during energy stress prompts its binding to high-affinity sites on the γ subunit, which facilitates exposure of Thr172 on the α subunit for phosphorylation.[116] AMP binding

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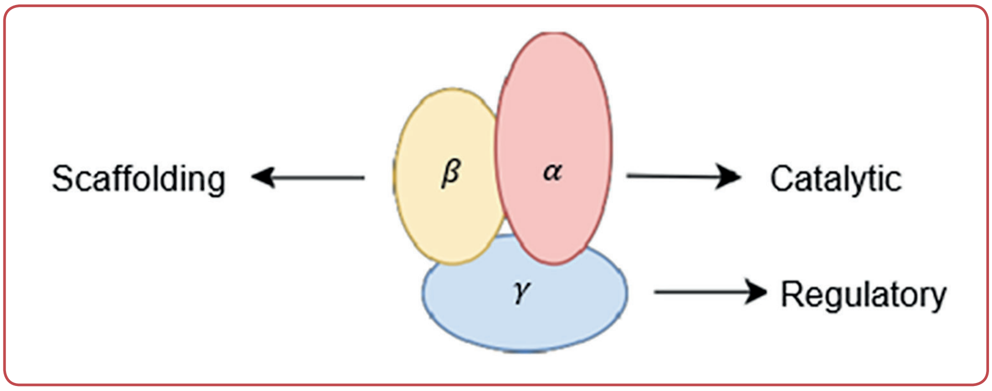

Figure 13: AMP-activated protein kinase (AMPK) structure
α subunit: Catalytic subunit containing kinase domain;
β subunit: Scaffolding role, bridges α and γ subunits;
γ subunit: Regulatory, binds AMP and ATP to sense energy status;

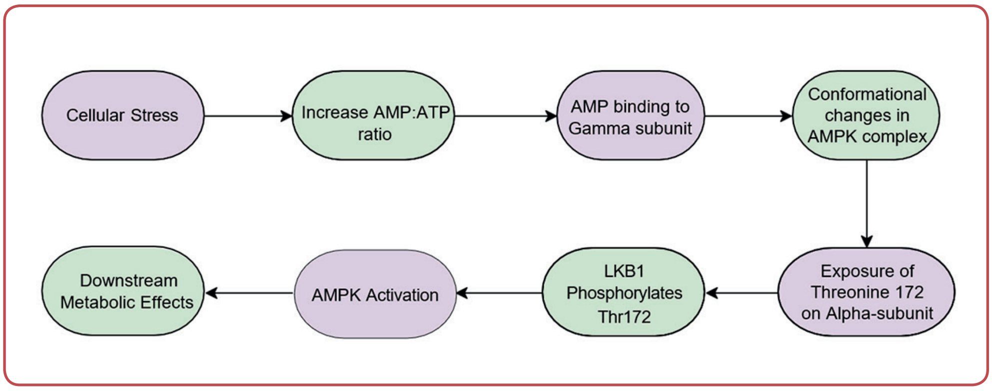

Figure 14: The AMP-activated protein kinase (AMPK) activation under cellular stress. AMP binds to the γ subunit, inducing structural changes that expose Thr172 on the α subunit. Liver kinase B1 (LKB1) phosphorylates this site, fully activating AMPK and triggering metabolic effects.

also prevents dephosphorylation, ensuring sustained activation of AMPK. Once phosphorylated by LKB1, AMPK adopts its active conformation.[117] Activated AMPK enhances catabolic processes such as fatty acid oxidation, glucose uptake and glycolysis, supporting cellular energy balance, especially important in diabetes management.[118]

Activation of AMPK pathway by *Brassica juncea*, *Gymnema sylvestre* and chromium picolinate drug

The AMP-activated protein kinase (AMPK) pathway plays a vital role in the regulation of glucose and lipid metabolism and is a key target in the management of diabetes mellitus. Both herbal and synthetic compounds have demonstrated the potential to activate this pathway. Natural constituents from *Gymnema sylvestre* and *Brassica juncea*, along with the chemical compound chromium picolinate, modulate metabolic processes via AMPK activation, which leads to phosphorylation and downstream metabolic benefits thereby contributing to improve glycaemic control. These include enhanced insulin sensitivity, suppression of hepatic gluconeogenesis, increased fatty acid oxidation and improved glucose uptake—collectively resulting in reduced blood glucose levels and better diabetes control, as shown in Figure 15.[119, 120]

Each of these compounds contributes uniquely to AMPK-mediated effects:

- *Gymnema sylvestre* provides gymnemic acid;
- *Brassica juncea* offers glucosinolates;
- Chromium picolinate contributes trivalent chromium (Cr^{3+}).
- Metabolic activation: These agents increase the AMP:ATP ratio, signalling an energy deficit that activates AMPK, a master regulator of cellular energy homeostasis.[121, 122] This activa-

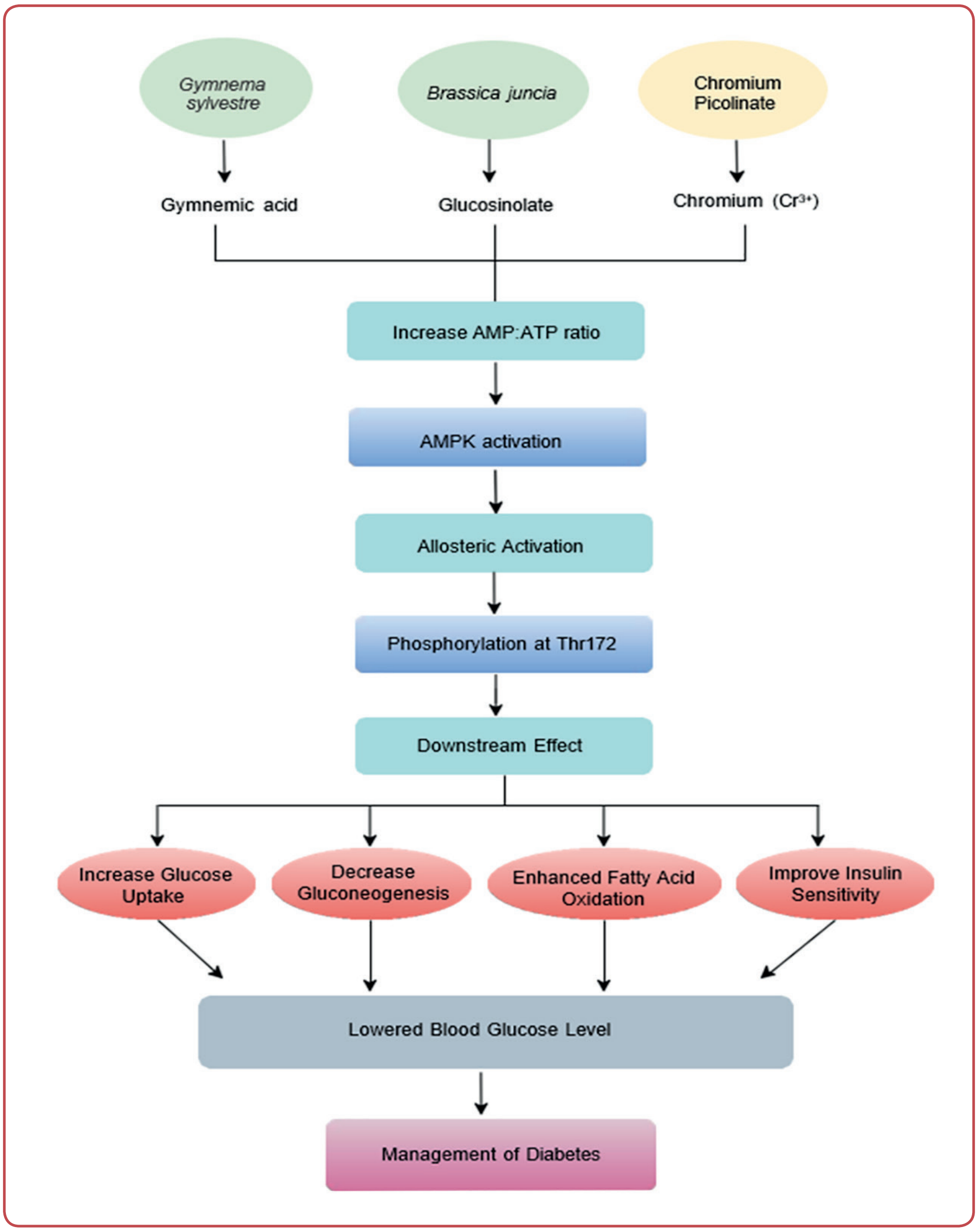

Figure 15: Chromium picolinate, Brassica juncea and Gymnema sylvestre support AMP-activated protein kinase (AMPK) activation leading to improved glucose metabolism and diabetes control

tion occurs through allosteric regulation and phosphorylation at threonine 172 (Thr172, a critical modification that maximises AMPK's activity.

- Downstream effects: Activated AMPK facilitates:
- Increased glucose uptake into cells;
- Reduced gluconeogenesis in the liver, decreasing endogenous glucose production;
- Enhanced fatty acid oxidation, improving lipid utilisation and reducing fat accumulation;
- Improved insulin sensitivity, making peripheral tissues more responsive to insulin.[123, 124]
- Outcomes: These biochemical changes result in lowered blood glucose levels, which are essential for effective diabetes management.
- Final goal: By enhancing energy regulation and metabolic efficiency, these compounds support long-term glycaemic control and metabolic health in diabetic patients.[125, 126]

Potential avenues for future exploration

Chromium picolinate, Gymnema sylvestre and *Brassica juncea* have demonstrated complementary mechanisms in enhancing insulin sensitivity, promoting hepatic enzyme activity and stimulating insulin secretion—collectively contributing to the management of diabetes mellitus.[33] These actions converge on the AMP-activated protein kinase (AMPK) pathway, a key regulator of cellular energy homeostasis, which yields metabolic benefits such as improved insulin responsiveness, suppression of hepatic gluconeogenesis and increased glucose uptake.[127] Future research should focus on clinical trials to validate the combined therapeutic efficacy of these agents in reducing blood glucose levels and improving overall metabolic parameters. Investigations into their long-term safety profiles and cost-effectiveness may support their integration into mainstream diabetes care.[128] Moreover, determining optimal dosages and synergistic ratios is essential to maximise therapeutic impact while minimising potential adverse effects. Additional studies should also assess their role in mitigating diabetes-related complications and promoting sustained metabolic health.[129]

Conclusion

The synergistic interaction of chromium picolinate, *Gymnema sylvestre* and *Brassica juncea* offers a comprehensive approach to managing diabetes mellitus. Chromium picolinate enhances insulin sensitivity and supports glucose metabolism by activating insulin signalling pathways. *Gymnema sylvestre* promotes pancreatic β-cell regeneration, increases insulin secretion and inhibits intestinal glucose absorption. In parallel, *Brassica juncea* aids in maintaining glucose homeostasis by stimulating hepatic enzymes that convert glucose into glycogen for storage.

Together, these bioactive compounds activate the AMPK pathway, a central regulator of cellular energy balance. This activation leads to metabolic adaptations such as enhanced glucose uptake by peripheral tissues, reduced hepatic gluconeogenesis, increased fatty acid oxidation and improved overall insulin responsiveness. These combined mechanisms contribute to a meaningful reduction in blood glucose levels, highlighting the therapeutic promise of these natural agents in diabetes control and broader metabolic health improvement.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2009 Jan;32 Suppl 1(Suppl 1):S62-7. doi: 10.2337/dc09-S062.
2. Fazakerley DJ, Krycer JR, Kearney AL, Hocking SL, James DE. Muscle and adipose tissue insulin resistance: malady without mechanism? J Lipid Res. 2019;6010:1720–32. doi: 10.1194/jlr.R087510.
3. Skarbez K, Priestley Y, Hoepf M, Koevary SB. Comprehensive review of the effects of diabetes on ocular health. Expert Rev Ophthalmol. 2010;54:557–77. doi: 10.1586/eop.10.44.
4. Low Wang CC, Hess CN, Hiatt WR, Goldfine AB. Clinical update: cardiovascular disease in diabetes mellitus—atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus: mechanisms, management and clinical considerations. Circulation. 2016;13324:2459–502. doi: 10.1161/CIRCULATIONAHA.116.022194.
5. Antar SA, Ashour NA, Sharaky M, Khattab M, Ashour NA, Zaid RT, et al. Diabetes mellitus: Classification, mediators and complications; a gate to identify potential targets for the development of new effective treatments. Biomed Pharmacother. 2023;168:115734. doi: 10.1016/j.biopha.2023.115734.
6. Tomic D, Shaw JE, Magliano DJ. The burden and risks of emerging complications of diabetes mellitus. Nat Rev Endocrinol. 2022;189:525–39. doi: 10.1038/s41574-022-00690-7
7. Ong KL, Stafford LK, McLaughlin SA, Boyko EJ, Vollset SE, Smith AE, et al. Global, regional and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2023;40210397:203–234. doi: 10.1016/S0140-67362301301-6.
8. Siam NH, Snigdha NN, Tabasumma N, Parvin I. Diabetes mellitus and cardiovascular disease: exploring epidemiology, pathophysiology and treatment strategies. Rev Cardiovasc Med. 2024;2512:436. doi: 10.31083/j.rcm2512436.
9. Murtaza G, Riaz S, Zafar M, Ahsan Raza M, Kaleem I, Imran H, et al. Examining the growing challenge: Prevalence of diabetes in young adults (Review). Med Int (Lond). 2025;51:2. doi: 10.3892/mi.2024.201.
10. Ling S, Zaccardi F, Issa E, Davies MJ, Khunti K, Brown K. Inequalities in cancer mortality trends in people with type 2 diabetes: 20-year population-based study in England. Diabetologia. 2023;664:657–73. doi: 10.1007/s00125-022-05854-8.
11. Iheagwam FN, Iheagwam OT. Diabetes mellitus: The pathophysiology as a canvas for management elucidation and strategies. Medicine in Novel Technology and Devices. 2025;25:100351. doi: 10.1016/j.medntd.2025.100351.
12. Koskinen MK, Helminen O, Matomäki J, Aspholm S, Mykkänen J, Mäkinen M, et al. Reduced β-cell function in early preclinical type 1 diabetes. Eur J Endocrinol. 2016;1743:251–9. doi: 10.1530/EJE-15-0674.
13. Di Giuseppe G, Ciccarelli G, Soldovieri L, Capece U, Cefalo CMA, Moffa S, et al. First-phase insulin secretion: can its evaluation direct therapeutic approaches? Trends Endocrinol Metab. 2023;344:216–30. doi: 10.1016/j.tem.2023.02.001.
14. Kahn BB. Type 2 diabetes: When insulin secretion fails to compensate for insulin resistance. Cell. 1998;925:593–6. doi: 10.1016/S0092-8674(0081125-3.
15. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of type 2 diabetes mellitus. Int J Mol Sci. 2020 Aug 30;21(17):6275. doi: 10.3390/ijms21176275.
16. Ye W, Luo C, Huang J, Li C, Liu Z, Liu F. Gestational diabetes mellitus and adverse pregnancy outcomes: systematic review and meta-analysis. BMJ. 2022;377:e067946. doi: 10.1136/bmj-2021-067946.
17. Choudhury AA, Devi Rajeswari V. Gestational diabetes mellitus – A metabolic and reproductive disorder. Biomed Pharmacother. 2021;143:112183. doi: 10.1016/j.biopha.2021.112183.
18. Zhou Z, Xu M, Xiong P, Yuan J, Zheng D, Piao S. Prognosis and outcome of latent autoimmune diabetes in adults: T1DM or T2DM? Diabetol Metab Syndr. 2024 Oct 7;16(1):242. doi: 10.1186/s13098-024-01479-6.
19. Makahleh L, Othman A, Vedantam V, Vedantam N. Ketosis-prone type 2 diabetes mellitus: an unusual presentation. Cureus. 2022;1410:e30031. doi: 10.7759/cureus.30031.
20. Serbis A, Kantza E, Siomou E, Galli-Tsinopoulou A, Kanaka-Gantenbein C, Tigas S. Monogenic defects of beta cell function: From clinical suspicion to genetic diagnosis and management of rare types of diabetes. Int J Mol Sci. 2024;2519:10501. doi: 10.3390/ijms251910501.
21. Parker VE, Semple RK. Genetics in endocrinology: genetic forms of severe insulin resistance: what endocrinologists should know. Eur J Endocrinol. 2013;1694:R71–R80. doi: 10.1530/EJE-13-0327.

22. Popoviciu MS, Paduraru L, Nutas RM, Ujoc AM, Yahya G, Metwally K, et al. Diabetes mellitus secondary to endocrine diseases: an update of diagnostic and treatment particularities. Int J Mol Sci. 2023;2416. doi: 10.3390/ijms241612676.
23. Fathallah N, Slim R, Larif S, Hmouda H, Ben Salem C. Drug-induced hyperglycaemia and diabetes. Drug Saf. 2015;3812:1153–68. doi: 10.1007/s40264-015-0339-z.
24. Mine K, Yoshikai Y, Takahashi H, Mori H, Anzai K, Nagafuchi S. Genetic susceptibility of the host in virus-induced diabetes. Microorganisms. 2020;88:1133. doi: 10.3390/microorganisms8081133.
25. Padhi S, Nayak AK, Behera A. Type II diabetes mellitus: a review on recent drug based therapeutics. Biomed Pharmacother. 2020;131:110708. doi: 10.1016/j.biopha.2020.110708.
26. Lorenzati B, Zucco C, Miglietta S, Lamberti F, Bruno G. Oral hypoglycemic drugs: pathophysiological basis of their mechanism of action. Pharmaceuticals (Basel). 2010;39:3005–20. doi: 10.3390/ph3093005.
27. LeRoy JM, Stellpflug SJ. Antidiabetic agents. In: Brent J, Burkhart K, Dargan P, Hatten B, Mégarbane B, Palmer R, Editors. Critical care toxicology. Cham: Springer International Publishing; 2016. p. 1–25.
28. The DCCT Research Group. Diabetes Control and Complications Trial (DCCT): results of feasibility study. Diabetes Care. 1987;101:1–19. doi: 10.2337/diacare.10.1.1.
29. Tamborlane WV, Ahern J. Implications and results of the Diabetes Control and Complications Trial. Pediatr Clin North Am. 1997;442:285–300. doi: 10.1016/S0031-3955(0570477-6.
30. Havel PJ. A scientific review: the role of chromium in insulin resistance. Diabetes Educ. 2004;Suppl:2-14. PMID: 15208835.
31. Wiernsperger N, Rapin J. Trace elements in glucometabolic disorders: an update. Diabetol Metab Syndr. 2010;21:70. doi: 10.1186/1758-5996-2-70.
32. Talab AT, Abdollahzad H, Nachvak SM, Pasdar Y, Eghtesadi S, Izadi A, et al. Effects of chromium picolinate supplementation on cardiometabolic biomarkers in patients with type 2 diabetes mellitus: a randomized clinical trial. Clin Nutr Res. 2020;92:97–106. doi: 10.7762/cnr.2020.9.2.97.
33. Wang ZQ, Yu Y, Zhang XH, Komorowski J. Chromium-insulin reduces insulin clearance and enhances insulin signaling by suppressing hepatic insulin-degrading enzyme and proteasome protein expression in KKAy mice. Front Endocrinol (Lausanne). 2014;5:99. doi: 10.3389/fendo.2014.00099.
34. Tiwari P, Mishra BN, Sangwan NS. Phytochemical and pharmacological properties of Gymnema sylvestre: an important medicinal plant. Biomed Res Int. 2014;2014:830285. doi: 10.1155/2014/830285.
35. Kanetkar P, Singhal R, Kamat M. Gymnema sylvestre: A memoir. J Clin Biochem Nutr. 2007;412:77–81. doi: 10.3164/jcbn.2007010.
36. Kannan P, Raghunathan M, Mohan T, Palanivelu S, Periandavan K. Gymnemic acid ameliorates pancreatic β-cell dysfunction by modulating Pdx1 expression: a possible strategy for β-cell regeneration. Tissue Eng Regen Med. 2022;193:603–16. doi: 10.1007/s13770-022-00435-7.
37. Ayadi J, Debouba M, Rahmani R, Bouajila J. Brassica genus seeds: A review on phytochemical screening and pharmacological properties. Molecules. 2022;2718:6008. doi: 10.3390/molecules27186008.
38. Rahman M, Khatun A, Liu L, Barkla BJ. Brassicaceae mustards: phytochemical constituents, pharmacological effects and mechanisms of action against human disease. Int J Mol Sci. 2024;2516:9039. doi: 10.3390/ijms25169039.
39. Ko DY, Seo SM, Lee YH, Gil CS, Lee H, Ku KM. Turning glucosinolate into allelopathic fate: investigating allyl isothiocyanate variability and nitrile formation in eco-friendly Brassica juncea from South Korea. Sci Rep. 2024;141:15423. doi: 10.1038/s41598-024-65938-w.
40. Coughlan KA, Valentine RJ, Ruderman NB, Saha AK. AMPK activation: a therapeutic target for type 2 diabetes? Diabetes Metab Syndr Obes. 2014;7:241–53. doi: 10.2147/DMSO.S43731.
41. Kakoti BB, Alom S, Deka K, Halder RK. AMPK pathway: an emerging target to control diabetes mellitus and its related complications. J Diabetes Metab Disord. 2024;231:441–59. doi: 10.1007/s40200-024-01420-8.
42. Li M, Ding L, Cao L, Zhang Z, Li X, Li Z, et al. Natural products targeting AMPK signaling pathway therapy, diabetes mellitus and its complications. Front Pharmacol. 2025;16:1534634. doi: 10.3389/fphar.2025.1534634.
43. Yuan X, Chen Z, Luo S, Xu X, Guo Y, Lin Y, et al. Photoinduced oxidation of chromium picolinate to hexavalent chromium in the presence of ferric ions. J Hazard Mater. 2024;477:135416. doi: 10.1016/j.jhazmat.2024.135416.
44. Sawicka E, Jurkowska K, Piwowar A. Chromium (III) and chromium (VI) as important players in the induction of genotoxicity—current view. Ann Agric Environ Med. 2021;281:1–7. doi: 10.26444/aaem/118228.
45. DesMarais TL, Costa M. Mechanisms of chromium-induced toxicity. Curr Opin Toxicol. 2019;14:1–7. doi: 10.1016/j.cotox.2019.05.003.
46. Ali A, Ma Y, Reynolds J, Wise JP Sr, Inzucchi SE, Katz DL. Chromium effects on glucose tolerance and insulin sensitivity in persons at risk for diabetes mellitus. Endocr Pract. 2011;171:16–25. doi: 10.4158/EP10131.OR.
47. Maleki V, Izadi A, Farsad-Naeimi A, Alizadeh M. Chromium supplementation does not improve weight loss or metabolic and hormonal variables in patients with polycystic ovary syndrome: a systematic review. Nutr Res. 2018;56:1–10. doi: 10.1016/j.nutres.2018.04.003.
48. Basiri R, Seidu B, Cheskin LJ. Key nutrients for optimal blood glucose control and mental health in individuals with diabetes: a review of the evidence. Nutrients. 2023;1518:3929. doi: 10.3390/nu15183929.
49. Jach ME, Serefko A, Ziaja M, Kieliszek M. Yeast protein as an easily accessible food source. Metabolites. 2022;121:63. doi: 10.3390/metabo12010063.
50. Vajdi M, Khajeh M, Safaei E, Moeinolsadat S, Mousavi S, Seyedhosseini-Ghaheh H, et al. Effects of chromium supplementation on body composition in patients with type 2 diabetes: A dose-response systematic review and meta-analysis of randomized controlled trials. J Trace Elem Med Biol. 2024;81:127338. doi: 10.1016/j.jtemb.2023.127338.
51. Henriksen C, Bügel S. Chromium – a scoping review for Nordic Nutrition Recommendations 2023. Food Nutr Res. 2023;67. doi: 10.29219/fnr.v67.10325.
52. Chromium supplementation and the essentiality of chromium to human nutrition: a narrative review. arXiv preprint arXiv:2309.10820. 2023. doi: 10.48550/arXiv.2309.10820.
53. Hua Y, Clark S, Ren J, Sreejayan N. Molecular mechanisms of chromium in alleviating insulin resistance. J Nutr Biochem. 2012;234:313–9. doi: 10.1016/j.jnutbio.2011.11.001.

54. Zhang W, Chen H, Ding Y, Xiang Q, Zhao J, Feng W, et al. Effect of chromium citrate on the mechanism of glucose transport and insulin resistance in Buffalo rat liver cells. Indian J Pharmacol. 2020;521:31–8. doi: 10.4103/ijp.IJP_608_18.
55. Li M, Chi X, Wang Y, Setrerrahmane S, Xie W, Xu H. Trends in insulin resistance: insights into mechanisms and therapeutic strategy. Signal Transduct Target Ther. 2022;71:216. doi: 10.1038/s41392-022-01073-0.
56. Clodfelder BJ, Emamaullee J, Hepburn DD, Chakov NE, Nettles HS, Vincent JB. The trail of chromium(III) in vivo from the blood to the urine: the roles of transferrin and chromodulin. J Biol Inorg Chem. 2001;65-6:608-17. doi: 10.1007/s007750100238.
57. Monga A, Fulke AB, Dasgupta D. Recent developments in essentiality of trivalent chromium and toxicity of hexavalent chromium: Implications on human health and remediation strategies. J Hazard Mater Adv. 2022;7:100113. doi: 10.1016/j.hazadv.2022.100113.
58. Kumpulainen JT. Chromium content of foods and diets. Biol Trace Elem Res. 1992;32:9–18. doi: 10.1007/BF02784582.
59. Masironi R, Wolf W, Mertz W. Chromium in refined and unrefined sugars: possible nutritional implications in the etiology of cardiovascular diseases. Bull World Health Organ. 1973;493:322–4. PMC2481154.
60. Hambidge KM. Chromium nutrition in man. Am J Clin Nutr. 1974;275:505–14. doi: 10.1093/ajcn/27.5.505.
61. Carlsen MH, Halvorsen BL, Holte K, Bøhn SK, Dragland S, Sampson L, et al. The total antioxidant content of more than 3100 foods, beverages, spices, herbs and supplements used worldwide. Nutr J. 2010 Jan 22;9:3. doi: 10.1186/1475-2891-9-3.
62. Wang H, Hu L, Li H, Lai YT, Wei X, Xu X, et al. Mitochondrial ATP synthase as a direct molecular target of chromium(III) to ameliorate hyperglycaemia stress. Nat Commun. 2023;141:1738. doi: 10.1038/s41467-023-37351-w.
63. Genchi G, Lauria G, Catalano A, Carocci A, Sinicropi MS. The double face of metals: the intriguing case of chromium. Appl Sci. 2021;112:638. doi: 10.3390/app11020638.
64. Song G, Tan H, Cheng C, Li P, Sun X, Zhou Y, et al. Development of a fast method using inductively coupled plasma mass spectrometry coupled with high-performance liquid chromatography and exploration of the reduction mechanism of Cr(VI) in foods. Toxics. 2024;125:325. doi: 10.3390/toxics12050325.
65. Zhitkovich A. Chromium in drinking water: Sources, metabolism and cancer risks. Chem Res Toxicol. 2011;2410:1617–29. doi: 10.1021/tx200251t.
66. Baghirov H. Mechanisms of receptor-mediated transcytosis at the blood-brain barrier. J Control Release. 2025;381:113595. doi: 10.1016/j.jconrel.2025.113595.
67. Thomsen MS, Johnsen KB, Kucharz K, Lauritzen M, Moos T. Blood-brain barrier transport of transferrin receptor-targeted nanoparticles. Pharmaceutics. 2022;1410:2237. doi: 10.3390/pharmaceutics14102237.
68. Devangan S, Varghese B, Johny E, Gurram S, Adela R. The effect of Gymnema sylvestre supplementation on glycemic control in type 2 diabetes patients: A systematic review and meta-analysis. Phytother Res. 2021;3512:6802–12. doi: 10.1002/ptr.7265.
69. Zamani M, Ashtary-Larky D, Nosratabadi S, Bagheri R, Wong A, Rafiei MM, et al. The effects of Gymnema sylvestre supplementation on lipid profile, glycemic control, blood pressure and anthropometric indices in adults: a systematic review and meta-analysis. Phytother Res. 2023;373:949–64. doi: 10.1002/ptr.7585.
70. Muzaffar H, Qamar I, Bashir M, Jabeen F, Irfan S, Anwar H. Gymnema sylvestre supplementation restores normoglycemia, corrects dyslipidemia and transcriptionally modulates pancreatic and hepatic gene expression in alloxan-induced hyperglycemic rats. Metabolites. 2023;134:516. doi: 10.3390/metabo13040516.
71. Kashif M, Nasir A, Gulzaman, Rafique MK, Abbas M, Ur Rehman A, et al. Unlocking the anti-diabetic potential of Gymnema sylvestre, Trigonella foenum-graecum and their combination thereof: an in-vivo evaluation. Food Sci Nutr. 2023;1112:7664–72. doi: 10.1002/fsn3.3685.
72. Bandala C, Carro-Rodríguez J, Cárdenas-Rodríguez N, Peña-Montero I, Gómez-López M, Hernández-Roldán AP, et al. Comparative effects of Gymnema sylvestre and berberine on adipokines, body composition and metabolic parameters in obese patients: a randomized study. Nutrients. 2024;1614:2284. doi: 10.3390/nu16142284.
73. Miranda DG, Tomé FM, Miguel MMV, Liberato S, Marcucci MC, Vigerelli H, et al. Gymnema sylvestre as a potential anti-inflammatory and anti-biofilm agent against anaerobic infections: an in vitro study. Plants (Basel). 2025;144. doi: 10.3390/plants14040497.
74. Mayyas A, Al-Samydai A, Oraibi AI, Debbabi N, Hassan SS, Al-Hussainy HA, et al. Deciphering the anti-diabetic potential of Gymnema sylvestre using integrated computer-aided drug design and network pharmacology. J Cell Mol Med. 2025 Jan;29(1):e70349. doi: 10.1111/jcmm.70349.
75. Nani A, Bertuzzi F, Meneghini E, Mion E, Pintaudi B. Combined inositols, α-lactalbumin, Gymnema sylvestre and zinc improve the lipid metabolic profile of patients with type 2 diabetes mellitus: a randomized clinical trial. J Clin Med. 2023;1224:7650. doi: 10.3390/jcm12247650.
76. Hechtman L. Polycystic ovary syndrome (PCOS). In: Pizzorno JE, Murray MT, editors. Textbook of natural medicine. 5th ed. St. Louis (MO): Churchill Livingstone; 2020. p. 1694–1706.e7.
77. Shivakumara KT, Chinapolaiah A, Keerthi MC, Ramya RS, Gotyal BS. Identification and characterization of novel resistant genotypes of Gymnema sylvestre (Retz.) R. Br. ex Sm. against invasive mealybug species, Phenacoccus solenopsis Tinsley and Paracoccus marginatus Williams and Granara de Willink for sustainable pest management. J Appl Res Med Aromat Plants. 2024;39:100534. doi: 10.1016/j.jarmap.2024.100534.
78. Pham HTT, Hoang MC, Ha TKQ, Dang LH, Tran VO, Nguyen TBT, et al. Discrimination of different geographic varieties of Gymnema sylvestre, an anti-sweet plant used for the treatment of type 2 diabetes. Phytochemistry. 2018;150:12–22. doi: 10.1016/j.phytochem.2018.02.013.
79. Sinsheimer JE, McIlhenny HM. Constituents from Gymnema sylvestre leaves. II. Nitrogenous compounds. J Pharm Sci. 1967;566:732–6. doi: 10.1002/jps.2600560615.
80. Shanmugasundaram ER, Gopinath KL, Shanmugasundaram KR, Rajendran VM. Possible regeneration of the islets of Langerhans in streptozotocin-diabetic rats given Gymnema sylvestre leaf extracts. J Eth-

nopharmacol. 1990;303:265–79. doi: 10.1016/0378-87419090106-4.
81. Neel S, Mandal A, Saha S, Das A, Kundu A, Singh A. Gymnema sylvestre saponins for potential antifungal action: in vitro and in silico perspectives. Front Plant Sci. 2025;16:1508454. doi: 10.3389/fpls.2025.1508454.
82. Sathya S, Kokilavani R, Gurusamy K. Hypoglycemic effect of Gymnema sylvestre (retz.,) R.Br leaf in normal and alloxan induced diabetic rats. Anc Sci Life. 2008 Oct;28(2):12-4. PMID: 22557305.
83. Turner S, Diako C, Kruger R, Wong M, Wood W, Rutherfurd-Markwick K, et al. Consuming Gymnema sylvestre reduces the desire for high-sugar sweet foods. Nutrients. 2020;124:1046. doi: 10.3390/nu12041046.
84. Jangam A, Tirunavalli SK, Adimoolam BM, Kasireddy B, Patnaik SS, Erukkambattu J, et al. Anti-inflammatory and antioxidant activities of Gymnema sylvestre extract rescue acute respiratory distress syndrome in rats via modulating the NF-κB/MAPK pathway. Inflammopharmacol. 2023;312:823–44. doi: 10.1007/s10787-022-01133-5.
85. Al-Romaiyan A, Liu B, Persaud SJ, Jones PM. A novel Gymnema sylvestre extract protects pancreatic beta-cells from cytokine-induced apoptosis. Phytother Res. 2020;341:161–72. doi: 10.1002/ptr.6512.
86. Liu M, Zhou T, Zhang J, Liao G, Lu R, Yang X. Identification of C21 steroidal glycosides from Gymnema sylvestre (Retz.) and evaluation of their glucose uptake activities. Molecules. 2021;2621:6549. doi: 10.3390/molecules26216549.
87. Netala VR, Hou T, Devarapogu R, Bethu MS, Zhang Z, Vijaya T. Exploring the therapeutic potential of triterpenoid saponins from Gymnema sylvestre: Mechanistic insights into hepatoprotection, immunomodulation, anticancer activities, molecular docking and pharmacokinetics. Heliyon. 2024;1023:e40850. doi: 10.1016/j.heliyon.2024.e40850.
88. Aditi SL, More P, Ghangale G, Tare H. Effect of Gymnema sylvestre in the control of diabetes: A review. Int J Pharm Qual Assur. 2023;141:214–9. doi: 10.25258/ijpqa.14.1.37.
89. Persaud SJ, Al-Majed H, Raman A, Jones PM. Gymnema sylvestre stimulates insulin release in vitro by increased membrane permeability. J Endocrinol. 1999;1632:207–12. doi: 10.1677/joe.0.1630207.
90. Abiola JO, Oluyemi AA, Idowu OT, Oyinloye OM, Ubah CS, Owolabi OV, et al. Potential role of phytochemicals as glucagon-like peptide 1 receptor (GLP-1R) agonists in the treatment of diabetes mellitus. Pharmaceuticals. 2024;176:736. doi: 10.3390/ph17060736.
91. Rahman MM, Dhar PS, Sumaia, Anika F, Ahmed L, Islam MR, et al. Exploring the plant-derived bioactive substances as antidiabetic agent: An extensive review. Biomed Pharmacother. 2022;152:113217. doi: 10.1016/j.biopha.2022.113217.
92. Di Fabio G, Romanucci V, Di Marino C, Pisanti A, Zarrelli A. Gymnema sylvestre R. Br., an Indian medicinal herb: traditional uses, chemical composition and biological activity. Curr Pharm Biotechnol. 2015;166:506–16. doi: 10.2174/1389201016061504071129 03.
93. Muddapur UM, Manjunath S, Alqahtani YS, Shaikh IA, Khan AA, Mannasaheb BA, et al. Exploring bioactive phytochemicals in Gymnema sylvestre: biomedical uses and computational investigations. Separations. 2024;112:50. doi: 10.3390/separations11020050.
94. Wen SY, Gao RR, Chen YY, Wang YJ, Wang XT, Liu HX. Brassinin from Brassica campestris L. inhibits colorectal cancer by inducing p62/NRF2/GPX4-regulated ferroptosis. Anim Model Exp Med. 2025. doi: 10.1002/ame2.12521.
95. Rizwan D, Masoodi FA. Brassica-derived isothiocyanates as anticancer therapeutic agents and their nanodelivery. Phytother Res. 2024 Jan;38(1):331-48. doi: 10.1002/ptr.8042.
96. Mandrich L, Caputo E. Brassicaceae-derived anticancer agents: Towards a green approach to beat cancer. Nutrients. 2020;123:868. doi: 10.3390/nu12030868.
97. Kim JS, Han S, Kim H, Won SY, Park HW, Choi H, et al. Anticancer effects of high glucosinolate synthesis lines of Brassica rapa on colorectal cancer cells. Antioxidants (Basel). 2022;1112:2463. doi: 10.3390/antiox11122463.
98. Kwak Y, Lee J, Ju J. Anti-cancer activities of Brassica juncea leaves in vitro. EXCLI J. 2016;15:699–710. doi: 10.17179/excli2016-586.
99. Batool U, Nawaz R, Ahmad S, Irshad MA, Irfan A, Gaafar ARZ, et al. Physico- and phytochemical properties of Brassica juncea as affected by agroclimatic conditions. Sci Rep. 2024;141:797. doi: 10.1038/s41598-023-48808-9.
100. Szőllősi R. Indian mustard (Brassica juncea L.) seeds in health. In: Preedy VR, Watson RR, editors. Nuts and seeds in health and disease prevention. 2nd ed. London: Academic Press; 2020. p. 357–64. doi: 10.1016/B978-0-12-818553-7.00025-5.
101. Das G, Tantengco OAG, Tundis R, Robles JAH, Loizzo MR, Shin HS, et al. Glucosinolates and omega-3 fatty acids from mustard seeds: Phytochemistry and pharmacology. Plants (Basel). 2022;1117. doi: 10.3390/plants11172290.
102. Sicard A, Thamm A, Marona C, Lee YW, Wahl V, Stinchcombe JR, et al. Repeated evolutionary changes of leaf morphology caused by mutations to a homeobox gene. Curr Biol. 2014;2416:1880–6. doi: 10.1016/j.cub.2014.06.061.
103. Retta MA, Van Doorselaer L, Driever SM, Yin X, de Ruijter NCA, Verboven P, et al. High photosynthesis rates in Brassiceae species are mediated by leaf anatomy enabling high biochemical capacity, rapid CO_2 diffusion and efficient light use. New Phytol. 2024;2445:1824–36. doi: 10.1111/nph.20136.
104. Baker RL, Yarkhunova Y, Vidal K, Ewers BE, Weinig C. Polyploidy and the relationship between leaf structure and function: implications for correlated evolution of anatomy, morphology and physiology in Brassica. BMC Plant Biol. 2017;171:3. doi: 10.1186/s12870-016-0957-3.
105. Tian Y, Deng F. Phytochemistry and biological activity of mustard (Brassica juncea): a review. CyTA J Food. 2020;181:704–18. doi: 10.1080/19476337.2020.1833988.
106. Torrijos R, Righetti L, Cirlini M, Calani L, Mañes J, Meca G, et al. Phytochemical profiling of volatile and bioactive compounds in yellow mustard (Sinapis alba) and oriental mustard (Brassica juncea) seed flour and bran. LWT. 2023;173:114221. doi: 10.1016/j.lwt.2022.114221.
107. Sheu MJ, Yeh MC, Tsai MC, Wang CC, Chang YL, Wang CJ, et al. Glucosinolates extracts from Brassica juncea ameliorate HFD-induced non-alcoholic steatohepatitis. Nutrients. 2023;1516:3497. doi: 10.3390/nu15163497.

108. Thirumalai T, Therasa SV, Elumalai EK, David E. Hypoglycemic effect of Brassica juncea (seeds) on streptozotocin-induced diabetic male albino rats. Asian Pac J Trop Biomed. 2011;14:323–5. doi: 10.1016/S2221-16911160052-X.
109. Farag MA, Goyal V, Baky MH. Comparative metabolome variation in Brassica juncea different organs from two varieties as analyzed using SPME and GC-MS techniques coupled to chemometrics. Sci Rep. 2024;141:19900. doi: 10.1038/s41598-024-69865-8.
110. Zhang B, Johnson MM, Yuan T, Nguyen TN, Okada J, Yang F, et al. Hepatic glycogen directly regulates gluconeogenesis through an AMPK/CRTC2 axis in mice. J Clin Invest. 2025;13511. doi: 10.1172/jci188363.
111. Al-Ishaq RK, Abotaleb M, Kubatka P, Kajo K, Büsselberg D. Flavonoids and their anti-diabetic effects: cellular mechanisms and effects to improve blood sugar levels. Biomolecules. 2019;99:430. doi: 10.3390/biom9090430.
112. Vaou N, Voidarou C, Rozos G, Saldari C, Stavropoulou E, Vrioni G, et al. Unraveling nature's pharmacy: transforming medicinal plants into modern therapeutic agents. Pharmaceutics. 2025;176:754. doi: 10.3390/pharmaceutics17060754.
113. Jadhav R, Das J, Rajyaguru S, Kyada S, Kale V, Teja PK, et al. Regulations, current development and future prospects of phytopharmaceuticals, a new class of herbal medicines in India. Discov Pharm Sci. 2025;11:6. doi: 10.1007/s44395-025-00006-4.
114. Aydin S, Tekinalp SG, Tuzcu B, Cam F, Sevik MO, Tatar E, et al. The role of AMP-activated protein kinase activators on energy balance and cellular metabolism in type 2 diabetes mellitus. Obes Med. 2025;53:100577. doi: 10.1016/j.obmed.2024.100577.
115. Safaie N, Masoumi S, Alizadeh S, Mirzajanzadeh P, Nejabati HR, Hajiabbasi M, et al. SGLT2 inhibitors and AMPK: The road to cellular housekeeping? Cell Biochem Funct. 2024;421:e3922. doi: 10.1002/cbf.3922.
116. Hawley SA, Russell FM, Ross FA, Hardie DG. BAY-3827 and SBI-0206965: potent AMPK inhibitors that paradoxically increase Thr172 phosphorylation. Int J Mol Sci. 2023;251. doi: 10.3390/ijms25010453.
117. Steinberg GR, Hardie DG. New insights into activation and function of the AMPK. Nat Rev Mol Cell Biol. 2023;244:255–72. doi: 10.1038/s41580-022-00547-x.
118. Fogarty S, Ross FA, Vara Ciruelos D, Gray A, Gowans GJ, Hardie DG. AMPK causes cell cycle arrest in LKB1-deficient cells via activation of CAMKK2. Mol Cancer Res. 2016;148:683–95. doi: 10.1158/1541-7786.MCR-15-0479.
119. Derosa G, D'Angelo A, Angelini F, Belli L, Cicero AFG, Da Ros R, et al. Nutraceuticals and supplements in management of prediabetes and diabetes. Nutrients. 2025;171:14. doi: 10.3390/nu17010014.
120. Wang YQ, Dong Y, Yao MH. Chromium picolinate inhibits resistin secretion in insulin-resistant 3T3-L1 adipocytes via activation of AMP-activated protein kinase. Clin Exp Pharmacol Physiol. 2009;368:843–9. doi: 10.1111/j.1440-1681.2009.05164.x.
121. Hoffman NJ, Penque BA, Habegger KM, Sealls W, Tackett L, Elmendorf JS. Chromium enhances insulin responsiveness via AMPK. J Nutr Biochem. 2014;255:565–72. doi: 10.1016/j.jnutbio.2014.01.007.
122. Viollet B. The energy sensor AMPK: adaptations to exercise, nutritional and hormonal signals. 2018 Mar 8. In: Spiegelman B, editor. Hormones, Metabolism and the benefits of exercise [Internet]. Cham (CH): Springer; 2017. PMID: 31314464.
123. Srivastava RA, Pinkosky SL, Filippov S, Hanselman JC, Cramer CT, Newton RS. AMP-activated protein kinase: an emerging drug target to regulate imbalances in lipid and carbohydrate metabolism to treat cardio-metabolic diseases. J Lipid Res. 2012;5312:2490–514. doi: 10.1194/jlr.R025882.
124. Garcia D, Shaw RJ. AMPK: mechanisms of cellular energy sensing and restoration of metabolic balance. Mol Cell. 2017;666:789–800. doi: 10.1016/j.molcel.2017.05.032.
125. Ke R, Xu Q, Li C, Luo L, Huang D. Mechanisms of AMPK in the maintenance of ATP balance during energy metabolism. Cell Biol Int. 2018;424:384–92. doi: 10.1002/cbin.10915.
126. Göransson O, McBride A, Hawley SA, Ross FA, Shpiro N, Foretz M, et al. Mechanism of action of A-769662, a valuable tool for activation of AMP-activated protein kinase. J Biol Chem. 2007;28245:32549–60. doi: 10.1074/jbc.M706536200.
127. Buccato DG, Ullah H, De Lellis LF, Morone MV, Larsen DS, Di Minno A, et al. Efficacy and tolerability of a food supplement based on Zea mays L., Gymnema sylvestre (Retz.) R.Br. ex Sm, zinc and chromium for the maintenance of normal carbohydrate metabolism: a monocentric, randomized, double-blind, placebo-controlled clinical trial. Nutrients. 2024;1615:2459. doi: 10.3390/nu16152459.
128. Li R, Zhang P, Barker LE, Chowdhury FM, Zhang X. Cost-effectiveness of interventions to prevent and control diabetes mellitus: a systematic review. Diabetes Care. 2010;338:1872–94. doi: 10.2337/dc10-0843.
129. Choudhury H, Pandey M, Hua CK, Mun CS, Jing JK, Kong L, et al. An update on natural compounds in the remedy of diabetes mellitus: a systematic review. J Tradit Complement Med. 2018;83:361–76. doi: 10.1016/j.jtcme.2017.08.012.