Revista Argentina de Clínica Psicológica
2024, Vol. XXX111, N°1, 54-73
DOI: 10.53555/03276716.2024.07

Harnessing Amygdalin In Integrative Medicine: Novel Insights For Endocrine Disorders

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ABSTRACT Amygdalin, often known as vitamin B17, is a cyanogenic glycoside that is mostly present in almond, cherry, and apricot seeds. The FDA has limited its usage in the United States because of its metabolism into hydrogen cyanide, which offers serious health hazards, even though it has historically been used for its alleged anticancer properties. Amygdalin and its derivatives, such as prunasin and mandelonitrile, may have pharmacological qualities, such as antiinflammatory and antioxidant benefits, notwithstanding these reservations. The complex pathophysiology of Polycystic Ovary Syndrome (PCOS), a common endocrine disorder characterized by hyperandrogenism and prolonged anovulation, includes inflammation as a major component in addition to hormonal and metabolic dysfunctions. Common in individuals, insulin resistance is linked to elevated levels of inflammatory markers such TNF-α, CRP, and IL-6. The therapy of PCOS may benefit from the use of interleukin-10 (IL-10), an antiinflammatory cytokine. Due to insulin resistance and other metabolic abnormalities linked to the disorder, PCOS and type 2 diabetes are significantly correlated. This mechanism involves the MAPK/ERK1/2 signaling pathway in addition to the crucial function of GLUT transporters in glucose metabolism. The possibility of cyanide poisoning raises concerns about amygdalin's safety, even though it may have therapeutic advantages for oxidative stress and reproductive health. To investigate its potential advantages while maintaining patient safety, more study is required.

KEYWORDS: Amygdalin, Laetrile, Vitamin B17, Cyanide, Anticancer properties, Polycystic Ovary Syndrome (PCOS), Insulin resistance, Chronic inflammation, Type 2 diabetes, Antioxidant properties

INTRODUCTION

Amygdalin sources (Vitamin B17):

Over time, proponents of natural medicine have come to recognize amygdalin, commonly known as "laetrile" and "vitamin B17," and research has suggested that it may have anticancer properties [1]. In the past thirty years, this vitamin has generated the greatest controversy. This cyanogenic plant glucoside, which is a member of the Rosaceae family, is discovered in the pits of many fruits and raw nuts, including almonds, cherries, peaches, plums, and apricot stones. Additionally, plants including sorghum, clover, and lima beans contain it [2]. The words laevorotatory and mandelonitrile are the sources of the word laetrile [1,3]. Mandelonitrile refers to a substance's chemical identity, whereas laevorotary defines stereochemistry. The chemical formula for amygdalin is C20H10NO11, and its estimated molecular weight is 457.42 Dalton. In the past, it was used to cure leprosy, leukoderma, asthma, and bronchitis [1]. Apricot kernels contain a chemical called amygdalin, which emits cyanide. Despite its dubious effectiveness and FDA warnings about cyanogenic dangers and a lack of clinical proof, amygdalin has been used globally, notably in the treatment of cancer [4]. During the 1920s, Dr. Ernst T. Krebs, Sr., a German scientist, conducted research on apricot kernel extract that contains amygdalin. This compound releases cyanide, which is harmful to humans because of its impact on intestinal bacteria. In 1952, his son, Krebs Jr., created 'laetrile', a substance structurally different from amygdalin. He later renamed it 'Vitamin B-17' in 1970[5]. Early studies focused on the potential anticancer effects of amygdalin and laetrile by examining the involvement of b-glucosidase in cancer cell activity [6]. According to Krebs Jr.'s theory, amygdalin releases more HCN when β-glucosidase levels in cancer cells are higher. Rhodanese, which detoxifies HCN and is present in both cancer and healthy cells, makes amygdalin's selective toxicity against cancer cells more difficult to achieve [7]. The theory put forth by Drs. Krebs and Krebs Jr., according to which glucosidase activity exclusively affects cancer cells, has also been proven to be incorrect because this enzyme has been detected in physiologically normal tissues, albeit in smaller quantities [8,9]. When the vitamin B-17 was given a new name in 1970, it attempted to get around the law prohibiting the use of pharmaceuticals. The usage of vitamins, particularly vitamin B-17, was prohibited [10]. In 1977, 23 states

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were prohibited from receiving laetrile and amygdalin from the U.S. food and drug agency (FDA) [11].

Chemistry and Enzymatic metabolism of Amygdalin:

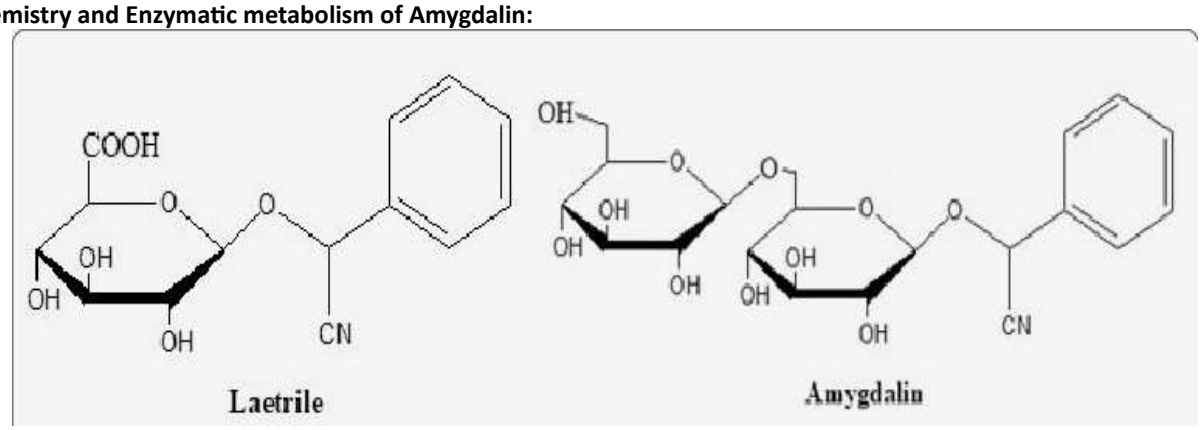

Figure: 1: - Biochemical Structural Illustration Coated with laetrile and amygdalin [12].

During the stage of fruit enlargement, amygdalin content typically increases and either stays constant or slightly declines as the fruit ripens. The endocarp of a peach seed has a higher concentration of amygdalin than the mesocarp. The cyanogenic amygdalin diglucoside concentration in almond kernels determines their bitterness [13]. The first step in the production of amygdalin is the conversion of L-phenylalanine to mandelonitrile, which is facilitated by cytochrome P450 and CYP71AN24. The enzyme UDP-glucosyltransferase transforms mandelenitrile into prunasin. Amygdalin is produced via the catalytic conversion of prunasin by the glucosyltransferase [14]. When tissue is macerated or digested, plants that contain cyanogenic glycosides (CGs) release hydrogen cyanide (HCN) through β-glycosidases and hydroxynitrile lyases, which may be inactivated by heat. In plants that lack β-glycosidases, several animals and humans depend on gut endosymbiotes for CG hydrolysis [15]. The bacterial flora in the intestine that can manufacture β-glycosidase in the brush border of the small intestine is likely responsible for the decisive synthesis of HCN in humans [16–18].

Amygdalin, the primary cyanogenic glycoside found in apricot kernels, 59 milligrams of hydrogen cyanide (HCN), which exists in its dissociated form as cyanide, are released when one gram of amygdalin is broken down. The fact that cyanide is extremely hazardous to people must be noted [19]. When orally consumed, amygdalin undergoes degradation by digestive enzymes during the salivary and gastrointestinal phases, resulting in the formation of prunasin as the main metabolite. β-glucosidase breaks down prunasin further to produce mandelonitrile. Amygdalase and prunase are examples of glucosidase enzymes that generate hydroxy mandelonitrile (149 Da) through hydroxylation across the small intestine wall. It eventually breaks down to produce hydrogen cyanide and benzaldehyde [20-22]. Despite not being hazardous in and of itself, amygdalin is broken down by certain enzymes to form the toxic chemical HCN [23]. According to recent studies, HCN is released in healthy cells, which could be harmful to the body [24]. The harmful effects of cyanide compounds are a result of the breakdown of amygdalin [25,26]. By attaching itself to a ferric ion in the mitochondrial cytochrome oxidase a3, cyanide prevents oxygen from being reduced to water, which inhibits cellular respiration [27]. The primary causes of cyanide poisoning are cellular hypoxia and disruption of aerobic cell metabolism, which lead to cardiovascular and central nervous system dysfunctions [28].

Pharmacological Activities of Amygdalin's derivatives

Table: 1 Amygdalin's derivatives with their pharmacological action

Derivative	Pharmacological Action	Reference(s)
Derivative	**Pharmacological Action**	
Prunasin	Anti-inflammatory, Antioxidant	[29]
Mandelonitrile	Anticancer, Antioxidant	[30]
Amygdalin Hydrolase	Enzyme, enhances amygdalin metabolism	[31]
N-Methyl-βphenylethylamine	Antidepressant, Neuroprotective	[32]
Phenylacetonitrile	Anticancer, Anti-inflammatory	[33]
Mandelic Acid	Antibacterial, Antifungal	[34]
L-Mandelonitrile	Anticancer, Antioxidant	[35]
Hydrocyanic Acid	Cytotoxic, used in controlled doses for specific treatments	[29]
Benzaldehyde	Anticancer, Antifungal	[34]
Amygdalin-7-O-glucoside	Antioxidant and anti-inflammatory effects	[36]
Amygdalin-2-O-acetate	Cardioprotective effects	[37]
Amygdalin-3-O-glucoside	Anti-diabetic effects	[38]

Biosynthesis of amygdalin:

A CYP79 enzyme hydroxylates the amino acid phenylalanine in amygdalin to phenyl acetaldoxime, which a CYP71 enzyme then further hydroxylates to mandelonitrile. The subsequent attachment of one glucose molecule to the α-hydroxyl group of mandelonitrile is catalyzed by a uridine diphosphate glucose-glucosyl transferase (UGT), producing prunasin (d-(-)-mandelonitrile-β-d-glucoside, CAS number 99-18-3, 295.3 g mol−1). When another glucose molecule is added to the 6'-hydroxyl group, it transforms into the di-glucoside gentiobiose, which is then converted to amygdalin (Figure 2). Plants produce amygdalin using the same basic process as CNGs, which involves cytochrome P450 (CYP) enzymes hydroxylating an amino acid to an oxime and then α-hydroxy nitrile, then glycosylating the latter [12].

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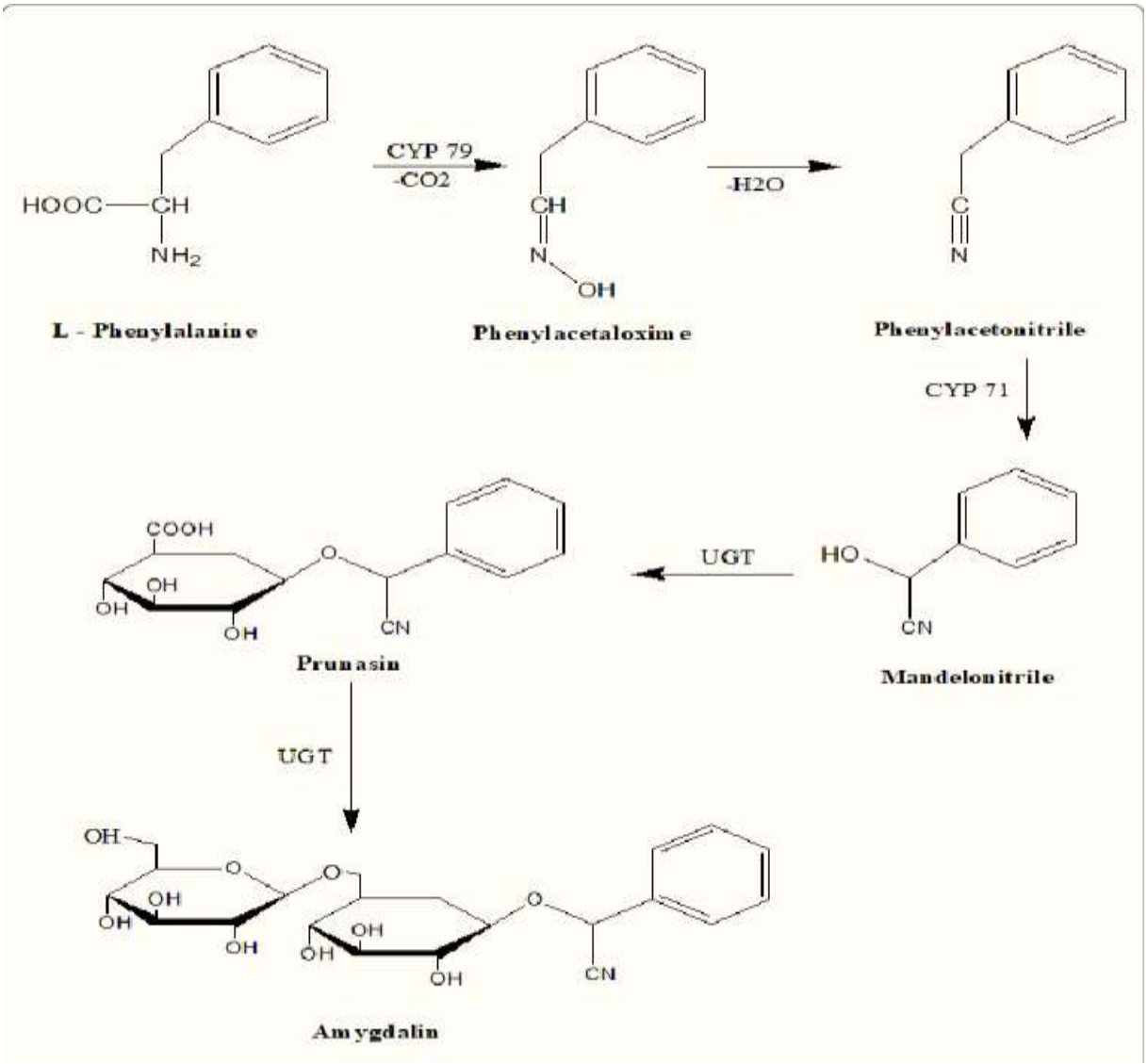

Figure: 2: - Amygdalin the process of biosynthesis is shown. [12].

Pharmacological Activities of drug in PCOS:

The condition known as The hallmarks of polycystic ovarian syndrome (PCOS) are hyperandrogenism and prolonged anovulation brought on by abnormalities in cellular regulation. Since the initial report by Stein and Leventhal, PCOS has been a subject of controversy in the field of gynecological endocrinology. Our knowledge of the endocrine processes underlying this syndrome's clinical symptoms is currently lacking, disjointed, and frequently unclear [39,40]. PCOS has been observed to run in families, with an autosomal dominant pattern of inheritance, suggesting an oligogenic basis. Several key genes have been implicated in the development of PCOS, including CYP11a, which affects androgen production, and insulin VNTR alleles, which influence hyperinsulinemia and associated risks such as menstrual irregularities and type 2 diabetes mellitus [41]. The pathophysiology of PCOS involves several hypotheses. The LH hypothesis suggests that there is exaggerated LH pulsatility, the insulin hypothesis proposes that insulin resistance leads to hyperinsulinemia, the ovarian hypothesis suggests excessive ovarian androgen production, and a fourth theory suggests a block in ovarian-level FSH activity despite a normal follicle response to FSH stimulation [42]. The widespread endocrine condition PCOS is not well understood pathophysiologically. It is thought to be the outcome of a convoluted "vicious cycle" with several beginning events that cause ovarian excess androgen production as well as anovulation. A main neuroendocrine malfunction resulting in an increased LH pulse frequency and amplitude; Hyperinsulinemia and resistance to insulin are caused by a specific abnormality in the action and secretion of insulin. An increase in adrenal production of androgenic due to a shift in cortisol metabolism; an increase in ovarian androgen production due to a failure in androgen synthesis [43].

Anti-Müllerian Hormone (AMH): Research on AMH and PCOS has been conducted. Granulosa cells in minor antral and preantral follicles produce AMH. AMH levels may be higher in PCOS individuals, particularly in those

who are obese, according to research. In addition to luteinizing hormone (LH) and antral follicle count, AMH can operate as a separate risk factor for the diagnosis of PCOS [44].

Glucose and Lipid Metabolism: In PCOS populations, glucose and lipid metabolism have a major impact on hormonal and associated parameters. Particularly in obese people, dysregulation of these metabolic pathways can make PCOS symptoms worse [44].

The Impact of GnRH in PCOS: An increasing amount of evidence suggests that increased

GnRH pulse frequency and intensity might promote the synthesis of LH rather than FSH, which would raise the LH/FSH ratio in PCOS-afflicted women [45]. The following data supports the idea that elevated LH levels play a critical role in the development of metabolic and reproductive problems. The first is that LH causes ovarian theca cells to produce more androgen, which results in hyperandrogenism and a stoppage of follicle growth [46]. Second, a higher frequency of LH pulses prevents the generation of FSH and estrogen, which delays ovulation and follicle development. Thirdly, the development of polycystic ovaries in PCOS patients is facilitated by LH, which increases ovarian IGF-1 release, which can improve LH binding and androgen synthesis in theca cells [47].

The etiology of PCOS, a common gynaecological endocrine condition in women of reproductive age, is still unclear. Its development is thought to be significantly influenced by inflammation, though. IL-6, TNF-α, IL-17, CRP, NLR, and PLR are among the inflammatory markers that have been studied in connection with PCOS. TNF-α is an inflammatory cytokine, while IL-6 is a protein of the immune system linked to inflammation. IL-17 has been linked to

PCOS, and CRP is a marker produced in response to inflammation. NLR indicates cardiovascular health and metabolic syndrome, while PLR has recently been associated with PCOS. It is noteworthy that the ratio of CRP to albumin can function as an accurate diagnostic for PCOS. Additionally, mean platelet volume (MPV) and PLR are also relevant indicators in this context [48-50].

Inflammatory markers related to PCOS:

Interleukins and their subtypes:

IL-6 (Interleukin-6):

Adipocytes from the body's fat reserves produce a multitude of cytokines, Interleukin 6, also known as IL-6, is among them [51]. PCOS is associated with higher IL-6 levels and are regulated by NF-κB. It is also associated with various diseases such as rheumatoid arthritis, cardiovascular conditions, asthma, and colon cancer, highlighting its dual pro- and antiinflammatory roles [52]. In its normal function, IL-6 supports epithelial renewal and immune function. However, in PCOS, insulin resistance may lead to increased IL-6 levels, indicating potential alterations in immunity and an increased risk of cardiovascular issues in young women [53]. Nevertheless, persistent inflammation caused by disorders like PCOS can pose significant dangers.

IL-8 (Interleukin-8):

IL-8, a cytokine that promotes inflammation, functions specifically as an activator and chemoattractant for neutrophils [54]. The role of IL-8 in regulating the ovary shows promise. It plays a part in the maturation of oocytes, ovulation, and follicular development [55]. According to earlier studies, the ovary's granulosa cells, stromal cells, and theca cells all contain IL-8 mRNA [56,57]. Goto et al. [58] have demonstrated that IL-8, as a signaling molecule, is involved in follicular development through vascularization. Research has documented the existence of IL-18 within the follicular fluid of patients undergoing in vitro fertilization (IVF) and females with regular menstrual cycles [59]. Ascites, blood, tumour tissue, and fluids from ovarian cysts in individuals with ovarian cancer have all been found to have elevated IL-8 levels [60,61]. Proliferation, adhesion, invasion, and angiogenesis are all improved by increased IL-8 expression [62]. Ovarian endometrium has increased IL-8 expression [63]. Serum IL-8 levels were linked to neo angiogenesis, metastasis, and melanoma, according to Nicolae et al. [64]. According to recent research, PCOS is associated with elevated IL-8 levels [65]. IL-8 was shown to be high in PCOS women in a clinical trial conducted by Ali et al. [66,67], but it reduced after receiving pioglitazone and metformin.

IL-10 (Interleukin-10):

The cytokine interleukin-10 (IL-10), which suppresses the immune system and reduces inflammation, is essential to our body's defensive systems [68]. It suppresses the activity of TH1 cells and was first discovered to be a component of TH2 cells [69]. It is thought to support the maintenance of pregnancy by reducing TH1 cell activity, which promotes progesterone production and corpus luteum maturation [70]. A low concentration of IL-10 has been associated with metabolic syndrome and obesity [71]. PCOS patients have shown a reduction in plasma IL-10 levels [72]. According to Sylus et al. [73], clomiphene citrate up-regulates IL10, causing PCOS women to ovulate and become pregnant at higher rates. Predicting the relationship between IL-10 and PCOS is difficult because the majority of research on the subject has been population-based [72,74] and has a limited sample size. The role of IL-10 in the pathophysiology of PCOS requires more investigation.

IL-17 (Interleukin-17):

Recent research has found a connection between PCOS and IL-17, IL-17a, and IL-1Ra [75– 77]. Inflammatory and autoimmune disorders are primarily affected by IL-17a [76]. Higher levels of IL-1Ra in PCOS affect glucose metabolism and lessen insulin resistance. Increases in

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inflammatory cytokines (IL-17a, IL-1a, IL-1b, IL-2, and IL-8) can impair ovarian activity, while high levels of AMH are associated with heightened inflammation and metabolic and reproductive dysfunctions [77].

TNF-α (Tumor Necrosis Factor-alpha):

Adipose tissue secretes TNF-α, IL-6, and adiponectin, with their levels being altered in cases of obesity. Changes in adipokine profiles can lead to a slightly proinflammatory condition that impacts both adipose tissue and other specific tissues [78,79]. TNF-α acts as a proinflammatory cytokine, By preventing the activity of tyrosine kinase of the receptor for insulin in fat and muscle cells, it contributes to the development of systemic resistance to insulin (IR), which is linked to obesity. On the other hand, adiponectin functions as an insulin sensitizer and possesses anti-inflammatory properties [80-82]. The pathophysiology of PCOS is associated with TNF-α due to its role in increasing insulin resistance (IR), causing hyperandrogenism (HA), and influencing follicular formation. It is thought that increased TNF-α expression in muscle tissue and Adipose tissue contributes to the development of IR in people by decreasing the activity of the tyrosine kinase of the insulin receptor [83,84]. Furthermore, TNF-α has been implicated in chronic inflammatory disorders such as ulcerative colitis, rheumatoid arthritis, and Crohn's disease [85-87]. Research has indicated that adiponectin expression may be reduced by TNF-α and IL-6. However, it is worth noting that TNF-α may also have the ability to increase adiponectin expression. In animal models, NF-κB, which is a pathway effector of TNF-α, has been linked to insulin resistance and metabolic disturbances associated with obesity [81]. In the case of PCOS, even in the absence of obesity, there is evidence of a proinflammatory environment that could be influenced by hyperandrogenism. This environment may contribute to the increased production of TNF-α by macrophages [88]. Females with PCOS have a greater amount of CRP (C-reactive protein) than people of the same age and BMI, which may indicate that PCOS has an underlying inflammatory mechanism [89,90]. The secretion of free fatty acid into the circulation by visceral adipocytes in non-obese women with PCOS has been found to assist modestly enhance inflammation in these individuals [81].

CRP (C-reactive protein):

The underlying cause of long-term cardiovascular hazards in PCOS may be persistent lowgrade inflammation. Obesity and insulin resistance contribute to dysfunction of endothelial cells, stiffness of the arteries, early ventricular alterations, and the onset of atherosclerosis, which may be brought on by oxidative stress, dyslipoproteinemia, hypertension, and disturbed homeostasis [91–93]. An raised white blood cell count, inflammatory cytokines including interleukin-6 and interleukin-18, and high levels of C-reactive protein (CRP) all point to a persistent state of low-grade inflammation that is characteristic of PCOS [93,94]. Research has indicated that C-reactive protein (CRP) is a very accurate predictor of cardiovascular morbidity and a dependable measure of inflammation [95,90,93], Specifically regarding lipid profile parameters [94]. Kalyan and colleagues discovered that the CRP/albumin ratio is a more accurate marker of inflammation in PCOS compared to free androgens or insulin resistance, demonstrating increased specificity regardless of BMI [96]. In PCOS, inflammation seems to play a significant role regardless of BMI, affected by CRP gene variations, which could be essential in confirming CRP as a reliable predictor of cardiovascular disease [97]. Theoretically, CRP might identify PCOS individuals who are more likely to develop heart disease and type II diabetes [93]. Just two published research articles have examined CRP level in PCOS patients and shown that they were more likely than controls to have increased CRP levels. These studies' authors came to the conclusion that women with PCOS had noticeably increased CRP levels [90,98]. They looked analysed levels of CRP in a larger cohort of PCOS patients who were matched with controls based on BMI in order to either support or refute this link.

NLR (Neutrophil-to-lymphocyte ratio):

NLR, a marker of inflammation, was utilized in PCOS [99-101]. In PCOS, NLR levels showed an increase even with comparable CRP values [100,101]. Inflammatory haematological indicators such as leucocytes, NLR, and PLR have been connected to the prediction of death from cancer, cardiovascular disorders, and cerebrovascular accidents [102-107]. NLR serves as an indicator of systemic inflammation [105].

PLR (Platelet-to-lymphocyte ratio):

PLR serves as a biological marker indicating thrombosis-inflammation balance. It correlates with increased megakaryocytic proliferation, thrombocytosis, and high platelet counts, alongside low lymphocyte counts, highlighting inflammation and clotting risks [106]. Activation of platelets and function are correlated with platelet size. Prior research has shown that MPV is a risk factor for cardiovascular illnesses and is a significant predictor of platelet activation [107]. The use of NLR, PLR, and MPV (mean platelet volume) as indicators of chronic inflammation is growing in the literature [105–107]. NLR [99–101] and MPV in PCOS [108–111] have been reported. PLR in PCOS hasn't been reported before, though. As far as we are aware, this article is the first to use NLR, PLR, and MPV in combination for PCOS. Furthermore, no research has looked at the relationship between inflammatory markers and PCOS IVF outcomes.

MAPK/ERK1/2:

The EMT process is regulated by the MAPK pathway, which is made up of many kinases like as p38, ERK1/2, and JNK [112]. The levels of JNK and p-JNK proteins, as well as the pJNK:JNK ratio, did not significantly differ across the patient groups. According to Western blot analysis, patients with PCOSEH and nPCOSEH showed higher p38 MAPK (MAPK) levels yet did not have p-p38 MAPK levels or p-p38:p38 ratios. Additionally, p-ERK1/2 and the p-ERK1/2:ERK1/2 ratio were greater in PCOS patients than in nPCOS patients, whereas p-ERK1/2 protein expression was also higher in nPCOSEH patients [113]. It has been demonstrated that IRS activation is suppressed by MAPK pathway activation, which encourages the formation of IR [114]. In the case of PCOS, MAPK signaling is a crucial signal transduction route connected to androgen production and IR [115]. Furthermore, decreased GLUT4 expression brought on by MAPK activation may hinder glucose transport [116]. Additionally, there is proof that PI3K/AKT signaling can affect the activation of the MAPK pathway [117]. We measured MAPK-related protein expression to determine if berberine's effects on IR were connected to MAPK pathway activation. In PCOS model mice, we found a substantial berberine-mediated inhibition of p38, ERK, and JNK. This implies that berberine may modulate the MAPK signaling pathway to attenuate IR in part. In conclusion, our study offers new proof that berberine therapy can reduce IR in a rat model system, hence mitigating the pathophysiology of PCOS through a mechanism most likely associated with GLUT4 overexpression. The molecular processes that underlie this increase are probably connected to the inhibition of MAPK signaling and the stimulation of PI3K/AKT signaling by berberine. Thus, our findings imply that berberine could have therapeutic uses. Crosstalk between MAPK signaling and PI3K-AKT is amply supported by prior research [118]. Our findings support the presence of this type of crosstalk and imply that it might be a major mediator of IR linked to PCOS.

GLUT And their Types:

Table: 2 GLUT Pathway and their role in PCOD and Diabetes:

GLUT TYPE	PATHWAY/ FUNCTION	ROLE IN PCOD	ROLE IN DIABETES	REFERENCES
GLUT1	Facilitates glucose uptake in most tissues	Elevated expression in ovarian tissues; linked to insulin resistance	Impaired expression contributes to glucose uptake issues	[119]
GLUT2	Highcapacity glucose transporter in liver, pancreas, kidneys	Implicated in glucose sensing and insulin release abnormalities	Dysfunction leads to hyperglycemia and reduced insulin secretion	[120]
GLUT3	Major transporter in neurons, placenta	May affect metabolic pathways influencing ovulation	Essential for glucose uptake in brain; dysfunction can impact cognition and metabolism	[121]
GLUT4	Insulinregulated glucose transporter in muscle and adipose tissue	Insulin resistance common in PCOD may lead to reduced GLUT4 activity	Deficiency linked to insulin resistance and Type 2 Diabetes	[122]
GLUT5	Fructose transporter	Potential link to metabolic syndrome in PCOD	May influence energy metabolism in diabetes	[123]

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JAK-STAT and JKT:

Table: 3 JAK-STAT and JKT (Janus Kinase Tyrosine) signaling Pathway and their role in PCOD and Diabetes:

PATHWAY	ROLE IN PCOS	ROLE IN DIABETES	REFERENCES
JAK-STAT	Inflammation, insulin resistanc e	Insulin signaling, betacell function	[124]
JKT	Insulin resistance, metabolic d ysfunction	Glucose metabolism, insulin s ensitivity	[125]

NOS And Their Types:

Table: 4 The roles of endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS) in PCOS and diabetes.

TYPE	ROLE IN PCOS	ROLE IN DIABETES	REFERENCES
iNOS	Inflammation, insulin resistance	Insulin resistance, impaired insuli n signaling	[126]
eNOS	Hormonal regulation, endotheli al function	Vascular homeostasis, atheroprote ction	[127]

TLRs Receptors and their roles in PCOD and Diabetes:

The innate immune system depends heavily on a family of proteins called toll-like receptors (TLRs). Immune responses are triggered by their recognition of pathogen-associated molecular patterns (PAMPs) [128].

Table: 5 TLRs Receptors and their types, their roles in PCOD and Diabetes:

TLR TYPE	ROLE IN PCOS	ROLE IN DIABETES	REFERENCE
TLR2	Inflammation, insulin resista nce	Insulin resistance, vascular comp lications	[129]
TLR4	Inflammation, hormonal imb alance	Insulin resistance, atherosclerosi s	[129]
TLR9	Inflammation, metabolic dys function	Insulin resistance, diabetic nephr opathy	130]

PCOS And Diabetes:

PCOS is a hormonal disorder marked by elevated levels of androgen hormones, which contribute to the development of male characteristics. Typical indications encompass the growth of facial hair, irregularity in menstrual cycles, acne, the presence of ovarian cysts, and difficulties with fertility [131].

Diabetes and Insulin resistance and their relation:

In women with polycystic ovarian syndrome (PCOS), the link between insulin resistance and hyperandrogenism is well-established [132]. Nevertheless, previous findings [133] indicating an insulin-antagonistic impact of androgens have been overshadowed by more recent research showing that antiandrogen therapy with flutamide [134] or GnRH agonists [135,136] does not modify insulin resistance in PCOS. Conflicting outcomes have been documented in non-PCOS females, with certain studies [132,137-140] proposing a link between testosterone and insulin resistance, while others [141,142] show no association. Despite this, androgens can impact body composition, which is linked to insulin sensitivity. Therefore, it is plausible that testosterone may indirectly affect insulin sensitivity through its influence on body composition. We present the findings of hormonal, metabolic, and body composition investigations conducted before, as well as 1 month and 9 months after, the removal of a Leydig cell tumor in a postmenopausal woman [143]. The correlation between PCOS and diabetes is significant, although PCOS itself does not directly cause diabetes. Resistance to insulin, a major contributing factor to the development of diabetes type 2, affects both illnesses [144]. PCOS is also linked to resistance to insulin, a condition in which the body fails to use insulin, the hormone that controls blood sugar levels, efficiently.

This illness makes type 2 diabetes more likely to occur [145]. A majority of individuals with PCOS experience some level of insulin resistance, although the exact percentage is unknown. Estimates suggest that approximately 65% to 70% of people with PCOS are insulin-resistant [146]. Insulin resistance and hyperinsulinemia are prevalent in 70% to 80% of individuals with PCOS who have a BMI over 30. However, even those with a lower BMI can be affected. The risk of insulin resistance is more strongly correlated with abdominal fat, indicated by a hip-to-waist ratio of 0.85 or higher, rather than BMI alone [147]. While PCOS may not directly cause diabetes, a study conducted in 2021 discovered that individuals with PCOS have a higher incidence of diabetes. However, this association may be attributed to shared risk factors rather than a direct cause and effect relationship [148]. Whether or not PCOS causes diabetes, it is important to remember that people with PCOS are more likely to get type 2 diabetes. A 2017 study found that body fat levels are linked to this increased risk of diabetes type 2, and that slim PCOS patients are not at a greater risk of developing type 2 diabetes [149]. An autoimmune response that stops insulin synthesis is known as type 1 diabetes [150]. Individuals with type 1 diabetes are at an increased risk of developing PCOS [151]. A comprehensive analysis and meta-analyses from 2016 recommend that individuals with ovaries and type 1 diabetes undergo screening for PCOS due to the heightened risk of developing PCOS and its associated traits [152].

Amygdalin and its Antioxidant effect:

Lipid production, protein folding, and calcium ion storage are only a few of the cellular functions in which the endoplasmic reticulum (ER) is essential [153]. Numerous illnesses, including overweight and obesity, atherosclerosis, diabetes type 2, hepatic cirrhosis, and renal damage, are strongly associated with ER stress [154]. Studies have demonstrated that disruptions in the ER homeostasis pathway lead to a decrease in very low-density lipoprotein levels, a rise in lipoprotein B100 breakdown and changes to transcription factors linked to lipids [155]. Transcriptional factors and enzymes involved in lipogenesis are overexpressed when ER stress is induced [156]. This can result in inflammation and apoptosis in the hepatic tissue [157]. Recently, The interaction of two cellular stressors, oxidative stress and ER stress, has drawn interest in the study of the pathophysiology of several illnesses [158,159]. Oxidative stress occurs when the body produces too many reactive oxygen species (ROS), which are products of oxygen molecules [160]. ROS can be generated by environmental factors or mitochondrial dysfunction [161]. Oxidative stress causes apoptotic cascades, releases inflammatory chemicals, and contributes to the development of a number of illnesses, including diabetes, non-alcoholic fatty liver disease, and kidney damage. According to a number of studies, the production of ROS within the ER is facilitated by unfolded proteins and abnormalities in the glutathione (GSH)/GSSH ratio during endoplasmic reticulum (ER) stress [162,163]. According to a research by Kim et al. [164], mice's livers showed reduced GSH levels and enhanced lipid peroxidation as a result of tunicamycin (TM)-induced ER stress. The overexpression of ER stress indicators, on the other hand, is linked to the enhancement of oxidative stress.

The ER stress cascade is triggered by oxidative stress, which also increases the production of C/EBP homologous protein (CHOP), activating transcription factor 4 (ATF4), and activating transcription factor 6 (ATF6) [165,166]. Ali et al [167] demonstrated that supplementation with GSH can effectively alleviate ER stress chaperones. In a separate investigation, selenium, known for its antioxidant properties, was found to downregulate the gene expressions of GRP78, ATF6, and ATF4. The levels of glutathione peroxidase (GSH-Px), catalase (CAT), and superoxide dismutase (SOD) were also shown to increase [168]. The cyanide-containing chemical amygdalin is often found in the seeds of apricots, peaches, bitter almonds, and other rosaceous plants. Because of its ability to block angiogenesis, cure conditions including emphysema, bronchitis, asthma, renal fibrosis, diabetes, and pain, amygdalin has been used historically [169-173].

Moreover, a number of investigations have demonstrated amygdalin's anti-inflammatory and anticancer properties in a range of cell lines and tissues [174–176]. During the first stage of this study, it was shown that amygdalin decreased the lipid profile, ALT, and AST levels in mice's livers during TM-induced ER stress [177]. Amygdalin decreased myeloperoxidase (MPO) and malondialdehyde (MDA) levels after D-galactosamine liver damage, according to a recent research by Tang et al. [178]. The purpose of this study was to assess the effects of amygdalin on oxidant and antioxidant markers in TM-induced ER stress and its relationship to ER stress and oxidative stress, since previous research has not examined the antioxidant qualities of amygdalin in the liver caused by ER stress and its association with oxidative stress. ER stress is linked to various conditions, such as diabetes. The antioxidant effects of amygdalin could potentially alleviate damage associated with ER stress [179].

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Table: 6 The application, model, dosage, key findings in tabular form:

APPLICATION	MODEL/SUBJECT	DOSAGE/FORM	KEY FINDINGS	REFERENCE
ANTI-INFLAMMATORY	Various cell lines	Various	reduces pro-inflammatory markers and cytokines to demonstrate antiinflammatory actions.	[180].
ANTICANCER	Cancer cell lines	Various	Induces apoptosis and inhibits proliferation in various cancer cell lines.	[183].
ANTIOXIDANT	Mice Liver	Pre-treatment, Moderate	Reduces MDA, increases SOD, CAT, GSH levels, and reduces oxidative stress.	[180].
DIABETES MANAGEMENT	Animal models	Various	Improves glucose tolerance and reduces blood glucose levels.	[182].
PAIN RELIEF	Various models	Oral, Intramuscular	Provides pain relief by modulating the central and peripheral nervous system.	[181].
ASTHMA AND BRONCHITIS TREATMENT	Animal models	Oral	Reduces inflammation and improves respiratory function in models of asthma and bronchitis.	[183].
HEPATIC PROTECTION	Mice Liver	Pre-treatment, Moderate	Reduces liver damage markers (ALT, AST), improves antioxidant status, and reduces lipid peroxidation.	[180].
RENAL FIBROSIS	Animal models	Various	Alleviates renal fibrosis by modulating oxidative stress and inflammation.	[182].
FEMALE REPRODUCTIVE HEALTH	Animal models	Various	Modulates oxidative balance in reproductive tissues, influences steroidogenesis, and supports reproductive health.	[181].
CARDIOPROTECTIVE EFFECTS	Animal models	Various	Reduces cardiac oxidative stress and improves cardiac function.	[183].

Cell lines and Targeting: -Amygdalin and their effects especially in PCOS and Diabetes: In India, the stem and leaves possess medicinal properties for the treatment of menstrual disorders and dysmenorrhea. The plant component contains a phytoconstituent that binds to estrogen receptors and effectively inhibits cell proliferation [184]. Polycystic ovarian disease, an endocrine disorder that causes menstrual irregularities due to hormonal imbalance affecting LH, FSH, estrogen, and testosterone levels, is significantly influenced by insulin resistance
[185]. The plant Scoparia dulcis, commonly referred to as sweet broom weed, belongs to the
Scrophulariaceae family of plants. It can be found in tropical and subtropical regions of India, Myanmar, America, and the West Indies [184,185]. This plant has been traditionally used for various medical purposes, such as managing diabetes, skin issues, kidney stones, menstrual disorders, anti-sickling, anti-cancer, and many other ailments [186]. S. dulcis demonstrates hypoglycaemic properties, improving the body's reaction to insulin and maybe helping to treat insulin resistance-related disorders, such as PCOD and ovarian tumors [187,188]. The aim of this study is to examine the possible anticancer properties of metformin, with a particular emphasis on its use in ovarian cancer (SKOV3 cell line), as well as the identification of plantderived compounds for further studies on inhibiting cell proliferation, which could be beneficial for PCOD treatment [189]. The chemical composition aided in the successful extraction and identification of Scoparia dulcis, as confirmed through analysis of the ethyl acetate extract. The extract's flavonoids and phenolic components were partly responsible for the suppression of SKOV3 ovarian cancer cells. The structural information on these compounds was acquired using HR-LCMS technique [190].

Safety and Side effects:

Cyanide Poisoning: Amygdalin is converted into cyanide within the body, and excessive consumption of amygdalin can result in cyanide poisoning. The following are symptoms of cyanide toxicity: vomiting, headaches, nausea light-headedness, fever, confusion, decreased blood oxygen levels that cause bluish discolouration of the lips and skin, Coma, death, nerve

damage, liver damage, and extremely low blood pressure [191,192].

Chronic Consumption: Neuropathy symptoms, such as blurred vision, hearing loss, unsteadiness, and malfunctioning sensory or motor nerves, can be brought on by a long-term diet high in cyanogenic glycosides (such as amygdalin)1 [191].

Conclusion:

The relationship between insulin resistance and inflammation is significant when PCOS, a condition characterized by hormonal and metabolic irregularities, is present. Antiinflammatory cytokines like interleukin-10 (IL-10) show potential in treatment options, however research indicates that PCOS patients often have high levels of inflammatory markers such TNF-α, CRP, and IL-6. These two disorders are correlated, which highlights the metabolic challenges faced by PCOS patients, which is related by processes involving the GLUT transporters and the MAPK/ERK1/2 signaling system. Vitamin B17, another name for amygdalin, is a substance that has both serious health hazards and some therapeutic advantages. It has been connected to anticancer effects and is present in seeds. Its conversion into hydrogen cyanide, however, raises questions about safety. The danger of cyanide poisoning cannot be disregarded, even considering amygdalin's possible anti-inflammatory and antioxidant properties. Therefore, further study is necessary to completely understand the compound's safety and efficacy, even if it may offer some therapeutic advantages in treating oxidative stress and reproductive health concerns. This data bolsters the idea that, in order to protect patient safety, any investigation into the advantages of amygdalin must be conducted under strict scientific examination.

Future prospective:

The study focuses on optimizing the dosage and safety of amygdalin, investigating its antioxidant, anti-inflammatory, and insulin-sensitizing effects, and designing rigorous clinical trials to evaluate its efficacy in treating PCOS and diabetes. It also explores the potential of combining amygdalin with other therapeutic agents to enhance its efficacy and safety profile. Personalized medicine is also explored, focusing on genetic and metabolic factors in individual responses to amygdalin treatment. Alternative derivatives of amygdalin, such as prunasin and mandelonitrile, are being researched to identify compounds with similar therapeutic benefits but lower toxicity. Public awareness and education are also being promoted, emphasizing the importance of controlled dosages and monitoring. Combining amygdalin with Novel Drug Delivery Systems (NDDS) could offer a new approach to managing Polycystic Ovary Syndrome (PCOS), targeting specific pathways while minimizing toxicity risks. Regulatory approvals are being established to ensure compliance with safety standards for the safe use of amygdalin and its derivatives.

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