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PHARMACOLOGY AND THERAPEUTICS – INNOVATIVE AND APPLIED CONCEPTS

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REVIEW BASED BOOK CHAPTER

UNLOCKING THERAPEUTIC POTENTIAL OF PHYTOCHEMICALS AGAINST NAFLD VIA TARGETING MITOCHONDRIAL DYSFUNCTION: A COMPREHENSIVE REVIEW

Ambreen Malik Uttra[1*], Sakeena Noor[1], Sumera Qasim[2], Muhammad Talha Raheem[3], Fakhria A. Al-Joufi[2]

[1]Department of Pharmacology, College of Pharmacy, University of Sargodha, Sargodha, Pakistan
[2]Department of Pharmacology, College of Pharmacy, Jouf University, 72341 Aljouf, Saudi Arabia
[3]Department of Electrical and Computer Engineering, COMSATS University Islamabad, Lahore Campus, Pakistan

For Correspondence
ambreen.malik@uos.edu.pk

Abstract

Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver conditions worldwide, and its incidence is still rapidly increasing. Nonetheless, there are still few effective treatments available for this liver condition. It has been established that NAFLD and mitochondrial dysfunction are closely related. Reactive oxygen species (ROS) are produced when mitochondrial damage occurs, and oxidative stress can exacerbate hepatic lipid buildup, inflammation, and fibrosis—all of which are factors in development and pathophysiology of nonalcoholic fatty liver disease (NAFLD). Consequently, pharmaceutical treatments that specifically target mitochondria may offer a viable means of intervening in NAFLD. Natural compounds that target mitochondria have been the subject of much research recently, and their pharmacological action appears promising. By summarizing the latest research on the therapeutic effects of compounds derived from natural products that target mitochondria and fight the disease, this chapter aimed to provide new therapeutic lead compounds and a point of reference for the innovative drug development and clinical treatment of nonalcoholic fatty liver disease (NAFLD).

Keywords

Non-alcoholic Fatty Liver, Mitochondrial Dysfunction, Insulin Resistance, Natural Compounds, Lipogenesis

1. Overview of NAFLD

Alcohol misuse or other secondary causes of chronic liver disease are not present in the case of non-alcoholic fatty liver disease (NAFLD), a disorder characterized by the accumulation of excess fat in the liver (hepatic steatosis) [1]. Non-alcoholic steatohepatitis (NASH), hepatic fibrosis, cirrhosis, liver fibrosis, and hepatocellular cancer are among the many liver diseases that fall under the umbrella of NAFLD [2]. NAFLD has two histological subtypes: nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver (NAFL). NAFLD is defined as ≥5% HS without hepatocyte ballooning, an indicator of hepatocellular injury. According to Chalasani et al. [3], NASH is defined by hepatocyte injury (ballooning) and inflammation with or without fibrosis (≥5% HS) [3]. According to Dharmalingam and Yamasandhi [4], NAFLD is linked with obesity and type 2 diabetes. Over 90% of those who are severely obese and up to 70% of overweight people have the condition. Lean subjects may also experience NAFL and NASH [5, 6]. When compared to non-Asians, Asians typically have higher degrees of ballooning and greater lobular inflammation than other ethnic groups [7]. Lower body mass can lead to fat buildup in the Asian population. Although the exact causes are unknown, NAFL and NASH are greater in Hispanics, intermediate in Whites, and lowest in Black individuals. The prevalence of NAFLD in kids and early teens is likewise rising. There isn't a single pharmaceutical therapy available to treat NAFLD. The lack of reliable non-invasive biomarkers and the complexity of the disease's pathogenic pathways may be the cause of NAFLD's multifactorial nature [8].

Furthermore, family investigations showed that NASH is definitely heritable. Overall, there is strong evidence that, relying on the ethnic origin, research protocol, and assessment techniques, between 20 and 70% of the variability in steatosis, as measured by either biochemical indices or noninvasive assessment, is familial [9]. Consequently, only a small percentage of NAFLD participants ever advance from steatosis to severe steatohepatitis, fibrosis, and hepato-carcinogenesis, which may

be largely explained by genetic predisposition. The comprehensive explanation has been carefully examined and condensed into a (Figure 1) [10].

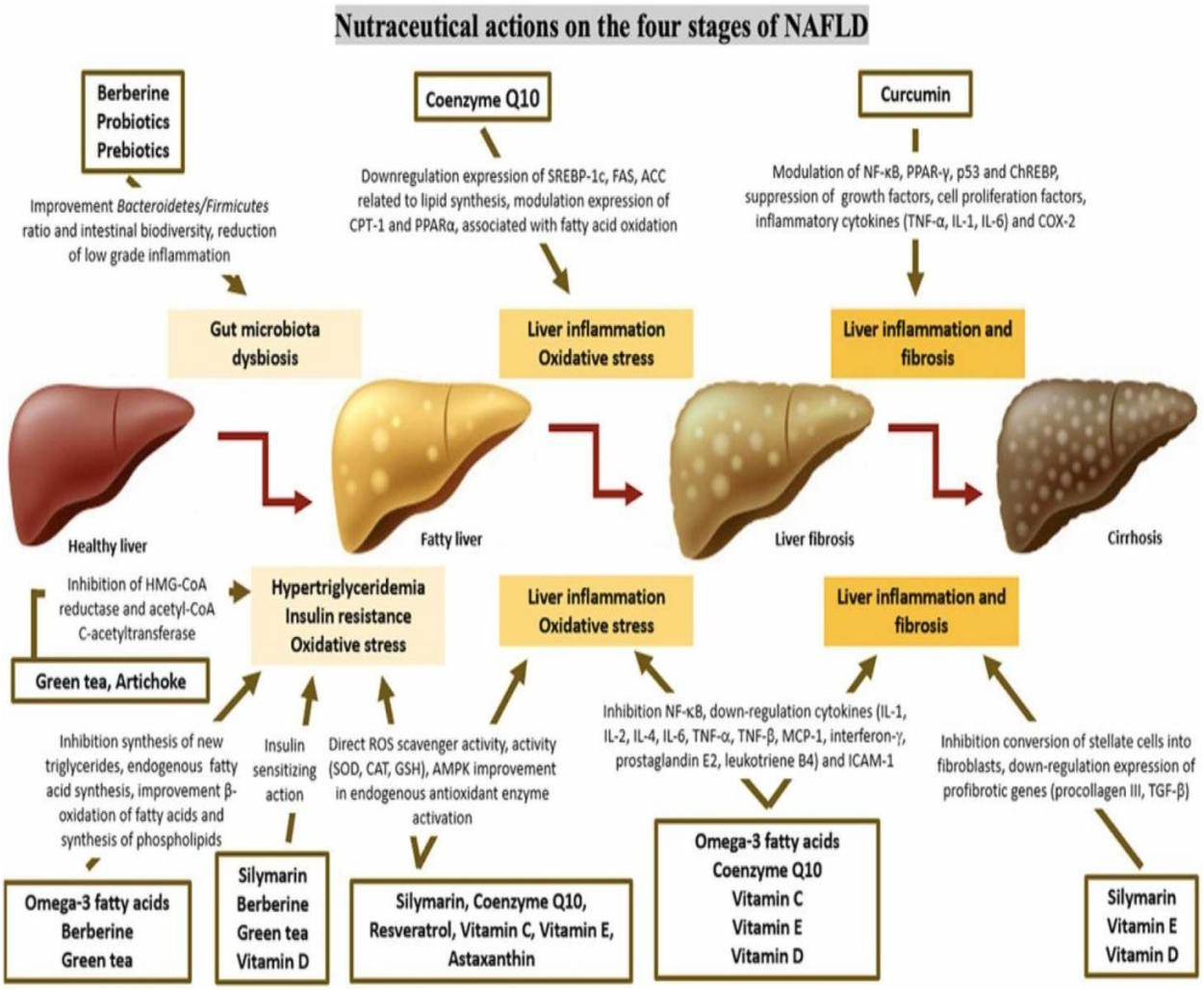

Figure 1: The elaboration of NAFLD (Adapted from Rizzo et al. [11])

2. Pathogenesis

It is unclear how exactly NASH develops because it is a complicated process. Animal research on the pathogenesis of NAFLD and NASH has been conducted extensively in the past several years. The main variations amongst the dietary models under investigation include high-fat, high-fructose, and methionine/choline deficient diets (MCD). Insulin resistance is made worse by the hepatic fat buildup that initiates this process [12]. This process's second phase entails cellular and

molecular alterations related to oxidative stress and the liver's fatty acid oxidation. This process is influenced by a number of variables, including cytokine damage, high insulin levels, hepatic iron and/or lipid peroxidation, extracellular matrix change, energy homeostasis, and altered immune system function [13]. Remarkably, it is thought that OS is caused by an excess of reactive oxygen species (ROS), which are created by Cytochrome P450 2E1(CYP2E1) in mitochondria and microcosms. A substantial amount of data indicates that mitochondrial malfunction results in aberrant CYP2E1 activation, which generates ROS and free radicals to cause inflammation and cause a variety of liver cell damage and death [12].

3. Lipid accumulation and toxicity

The liver is crucial to the body's lipid (fat) metabolism, which turns extra glucose into fat for storage and breaks down fat for energy. This process helps the body maintain homeostasis. Less than 5% of healthy liver cells should be fat [1]. Lipids are the reserve of extra energy when energy intake exceeds energy use. Increased circulating levels of FFA and TGs, as well as TGs deposited in adipose tissue, all contribute to peripheral IR in a disordered state. In obese individuals, compensatory hyperinsulinemia and prolonged hyperglycemia accelerate the development of T2D and fatty liver [14].

Significant increases in plasma FFA excess brought on by IR because mitochondrial damage in hepatocytes, which produces a lot of ROS and triggers inflammatory reactions, oxidative stress, and ER stress. Excessive triglyceride (TG) synthesis in hepatocytes is the reason of hepatic steatosis in NAFLD patients (Figure 2) [15].

Insulin may boost the body's synthesis of fat. In it, two transcription factors are crucial. The proteins carbohydrate response element binding protein (ChREBP) and sterol regulatory element binding protein 1 (SREBP-1). The former is thought to be the primary modulator of the production of fatty acids. One of the primary isoforms of SREBP-1, known as sterol regulatory element-binding protein 1c (SREBP1c), blocks the β-oxidation of FFA via nuclear receptor peroxisome proliferator-activated

receptor alpha (PPAR-a), but boosts the fatty tissue formation of glucose and free fatty acids circulation to the liver by means of peripheral resistance to insulin [16].

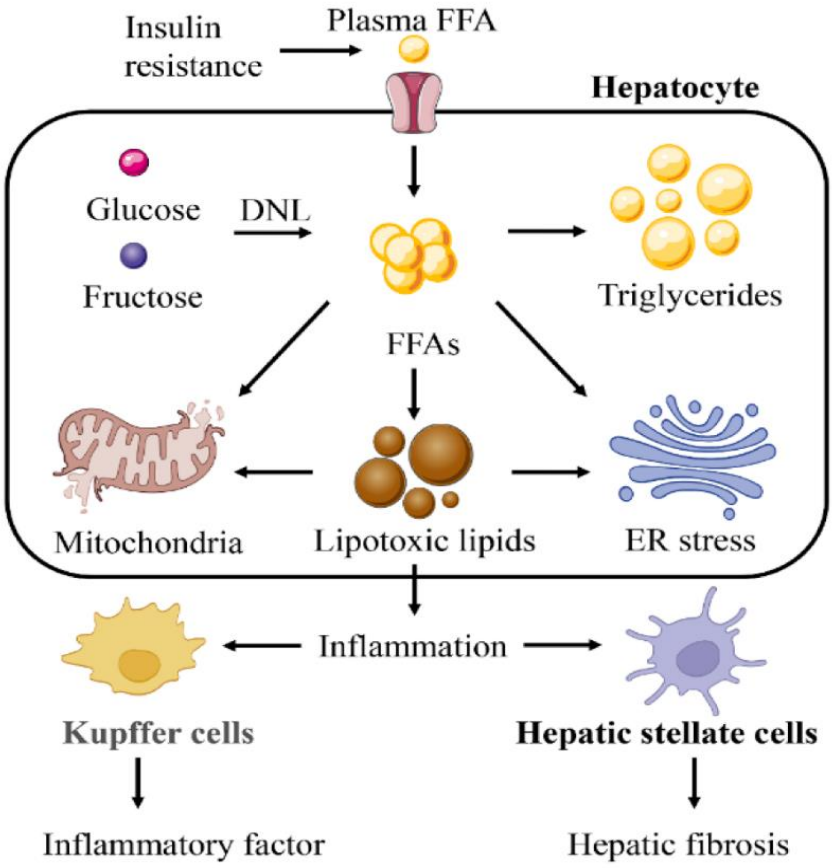

Figure 2: Lipotoxicity producing Inflammatory reactions and hepatic fibrosis (Adapted from Guo et al. [15])

4. Mitochondrial dysfunction and oxidative stress

When it comes to the quantity and density of mitochondria, the liver is among the richest organs. Damaged mitochondria accumulate in the majority of chronic liver disorders. The mitochondria in the liver are different from those in other organs because they serve as the center for the metabolism of proteins, lipids, and carbohydrates in the liver and are crucial for the survival of hepatocytes by acting as mediators of necrosis and apoptosis [17]. Numerous physiological processes, including the creation of adenosine triphosphate (ATP), the fabrication of free

radicals, the oxidation of fatty acids, calcium homeostasis, and cell survival and death, are regulated by mitochondria [18].

ROS overproduction, oxidative stress, and respiratory chain decrease are the primary markers of mitochondrial malfunction. The development of NAFLD is intimately linked to these outcomes in terms of lipid buildup, inflammation, and hepatic cell death. Accordingly, NAFLD is seen as a particular kind of mitochondrial disease [19].

Notably, OS has a role in general progression of non-alcoholic fatty liver disease (NAFLD). OS causes by plenty of reactive oxygen species (ROS), which are formed in mitochondria by cytochrome P450 2E1 (CYP2E1), as shown in Figure 3 [12]. Several investigations have demonstrated that abnormal CYP2E1 activation brought on by mitochondrial malfunction promotes OS and lipid peroxidation (LPO) via generating free radicals and ROS. According to a number of studies, CYP2E1 may contribute to the excessive buildup of fat and exacerbate OS, which can cause inflammation, damage to liver cells, and even mortality [12]. According to Jian et al. [20], this effect is linked to the persistent activation of C-jun N-terminal kinase (JNK) signaling cascades, which advanced hepatocellular damage and micro-vesicular steatosis. It is evident that treating NAFLD requires the development of drugs that block CYP2E1 upregulation [12, 20].

There exist multiple potential mechanisms linking mitochondrial ROS and insulin resistance. Mitochondrial ROS first phosphorylate the IRS protein and decrease the activity of serine/threonine phosphatase, which in turn blocks the insulin signaling pathway [21]. Moreover, via raising serine phosphorylation of IRS-1, lowering insulin-stimulated tyrosine phosphorylation of IRS-1, and activating c-jun NH2-terminal kinases (JNK) and apoptotic signal-regulating kinase 1 (ASK1), mitochondrial ROS lead to insulin resistance. But those pathways are just now being supported by the limited experimental data that is now available, and extended research is still required to fully comprehend the precise mechanism of mitochondrial ROS-

induced insulin resistance [18]. Long-term oxidative stress not only leads to mitochondrial dysfunction but also activates signaling pathways related to inflammation, such as JNK and NF-κB. This can result in the release of inflammatory cytokines from cells, infiltration of inflammatory cells, or even death of parenchymal hepatic cells [6]. For example, elevated TNF-a can cause mitochondrial lipid peroxidation, activate the membrane permeability transition, and release cytochrome C, which leads to hepatocyte necrosis or apoptosis, which is labeled as a major step in the manifestation of NASH (Figure 4) [19].

Numerous hits contribute to the onset of NAFLD/NASH and its development into hepatocellular carcinoma HCC. Numerous signaling pathways linked to metabolic stress, such as free fatty acids, ER-stress, cytokine production (IL-6, IL-17, IL-11, and TGF-β), altered immune response, pro-fibrogenic mediators (hedgehog and NF-κB), gut dysbiosis, and endocrine abnormalities, are responsible for the development of NAFLD/NASH-associated HCC [22].

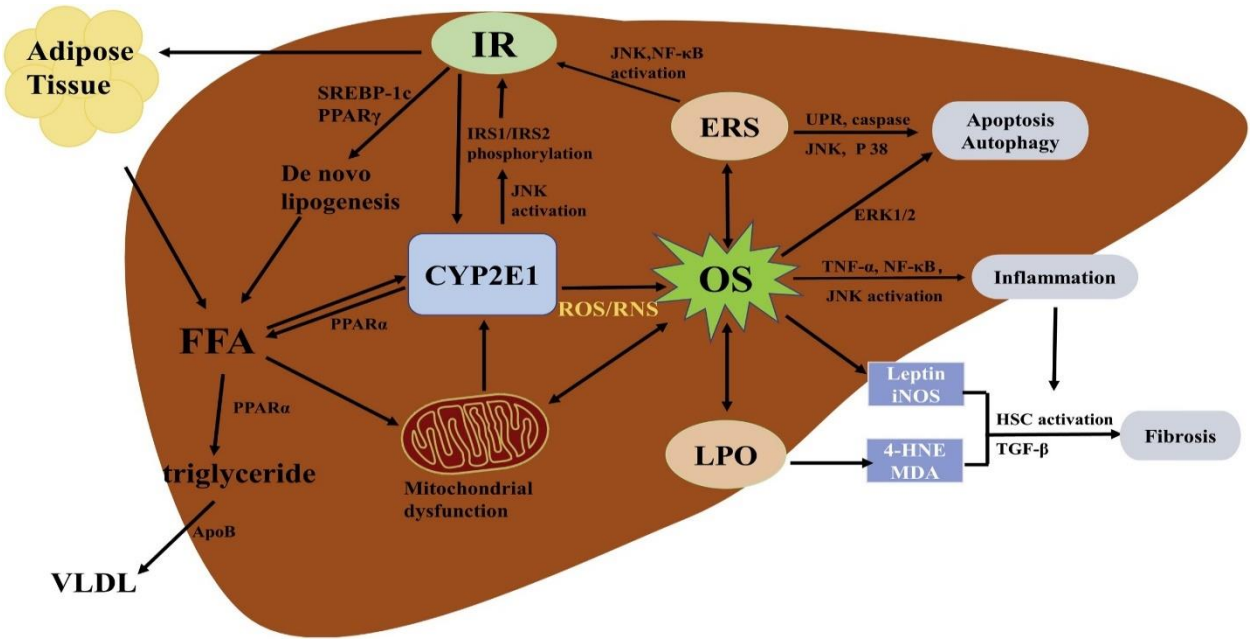

Figure 3: Upregulation of CYP 2E1 promotes the development of NAFLD (Adapted from Wang et al. [12])

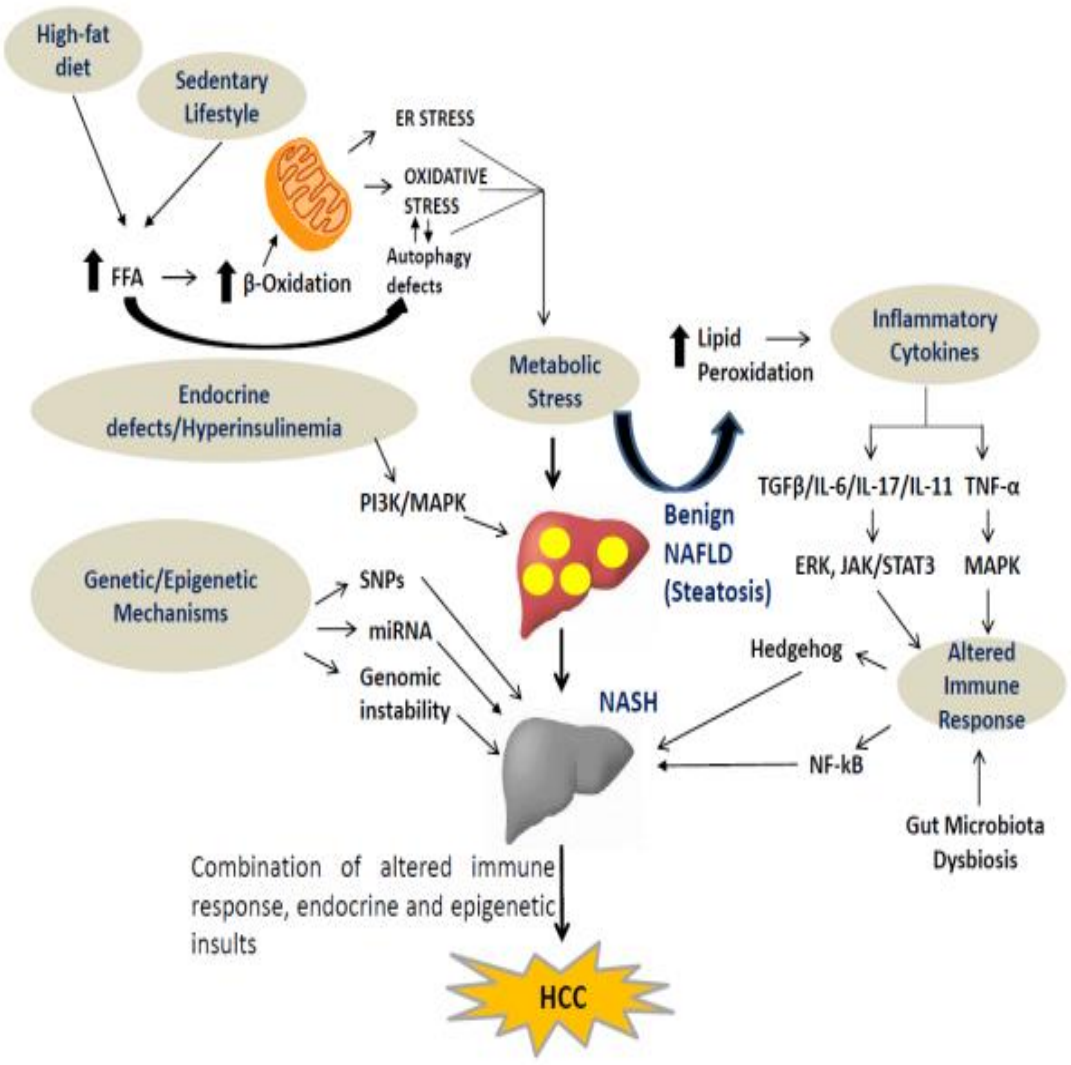

Figure 4: Multiple strikes cause NAFLD/NASH to begin and progress toward HCC (Adapted from Xu et al., [19])

5. Phytochemicals that target the mitochondrial dysfunction in NAFLD

Plants create bioactive molecules known as phytochemicals to defend themselves. More than a thousand phytochemicals have been found to date, and they can be obtained from a variety of foods, including whole grains, fruits, vegetables, nuts, and herbs [23]. Phytochemicals are quite interesting and have a lot of antioxidant potential because of their beneficial effects on human health and the significant health benefits they provide for customers. According to epidemiological study and

animal studies, eating fruits, vegetables, and whole-grain foods on a regular basis may reduce the risk of several diseases that are associated with oxidative damage [24]. A growing body of research indicates that natural products may enhance mitochondrial function and ameliorate related metabolic disorders, such as diabetes, fatty liver disease (NAFLD), and consequences from diabetes. Natural medicine is becoming a supplemental option for the prevention and treatment of NAFLD because of its low toxicity and adverse effects. According to estimates, natural substances or their derivatives make up 40% of FDA-approved therapies [19]. Natural products with strong anti-inflammatory and antioxidant properties include terpenoids like tripterine and triptolide, phenolic compound curcumin, and terpenoid berberine. These properties may find use in the treatment of liver diseases associated with mitochondrial dysfunction (Figure 5) [25].

Aramchol (Arachidyl-amido cholanoic) did not enhance insulin sensitivity, hepatic enzymes, or glucose metabolism, but it did show promise in treating hepatic steatosis in humans. By lowering stearoyl coenzyme-A desaturase 1 (SCD1) and increasing fluxes that preserve cellular redox equilibrium via the transsulfur route, aramchol improves fibrosis and steatohepatitis in animal models. In several tissues, including the liver, mice lacking SCD1 exhibit decreased lipid production, elevated mitochondrial FA β-oxidation, and insulin sensitivity. Thus, in a number of nonalcoholic fatty liver mouse models, including high carbohydrate and HFD animals, SCD1 deficiency has been linked to the prevention of hepatic steatosis [14].

5.1. Phenolics

According to Saha et al. [26], phenolic compounds are recognized for their various chemical structures, shared antioxidant properties, and particular anti-inflammatory properties. While triglyceride buildup in the liver was found to be somewhat reduced by all polyphenols or polyphenol-rich extracts, each studied chemical may have a unique molecular target [2]. Two types of polyphenols are distinguished by their chemical structures: flavonoids, which include flavones, flavanols, flavonols,

isoflavones, proanthocyanidins, and anthocyanins; and non-flavonoids, which include hydroxytyrosol and stilbene phenolic acids, which include resveratrol [27]. The regulation of lipidogenesis, insulin resistance modulation, oxidative stress modification, and inflammation management were among the mechanisms of action [2].

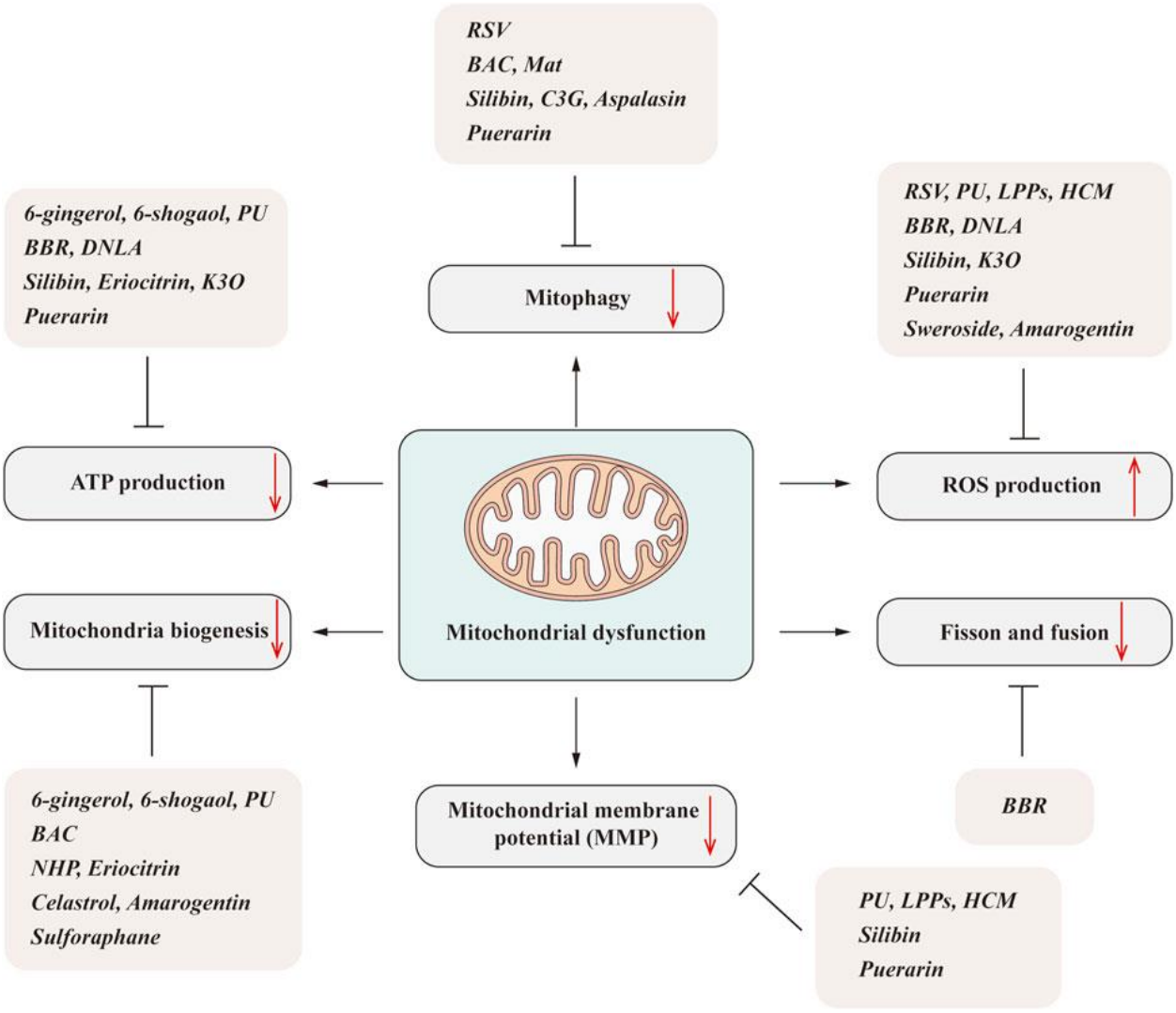

Figure 5: Natural products ameliorate NAFLD by regulating mitochondrial dysfunction (Adapted from Xu et al., [19])

Figure 6 illustrates the various mechanisms by which polyphenols may protect hepatocytes linked to non-alcoholic fatty liver disease (NAFLD) from cellular

damage. These mechanisms include: (a) lowering de novo lipogenesis by down-regulating sterol regulatory element-binding protein 1c (SREBP-1c); (b) raising β-fatty acid (FA) oxidation by up-regulating PPARa; (c) enhancing insulin sensitivity; (d) lowering oxidative stress by raising antioxidant levels via nuclear factor-erythroid 2-related factor 2 (Nrf2); and (e) attenuating the inflammatory pathways. The down-regulation of SREBP-1c and the up-regulation of PPARa are likely influenced by the activation of AMPK through phosphorylation [28, 29].

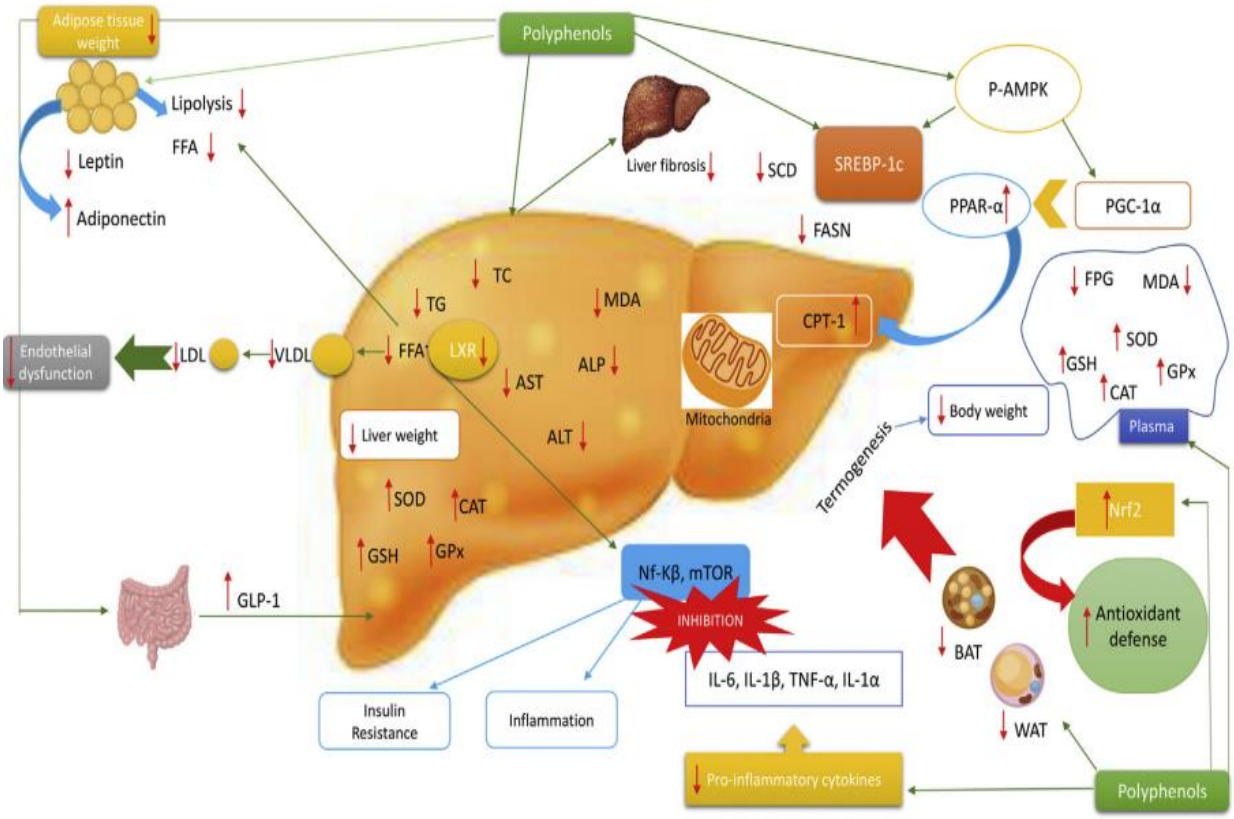

Figure 6: Possible mechanism of polyphenols effect on NAFLD (Adapted from Bayram et al., [28])

5.2. Alkaloids

Alkaloids are nitrogenous organic compounds with an alkaline polarity that are commonly found in natural plants. According to Cheng et al. [30], the majority of alkaloids show notable actions in lipid metabolism and have complicated cyclic

structures. Alkaloids are nitrogen oxides with a bitter taste that are often colorless and present in plants, particularly in seeds [30]. The broad array of pharmacological properties that alkaloids possess, such as their anti-inflammatory, analgesic, anti-tumor, antioxidant, and antibacterial properties, make them advantageous instruments for drug creation. Alkaloids primarily alleviate NAFLD by preventing hepatic steatosis and having anti-inflammatory and antioxidant properties [16]. Figure 7 presents the mechanism of action of various bioactive phyto-constituents against NAFLD [31].

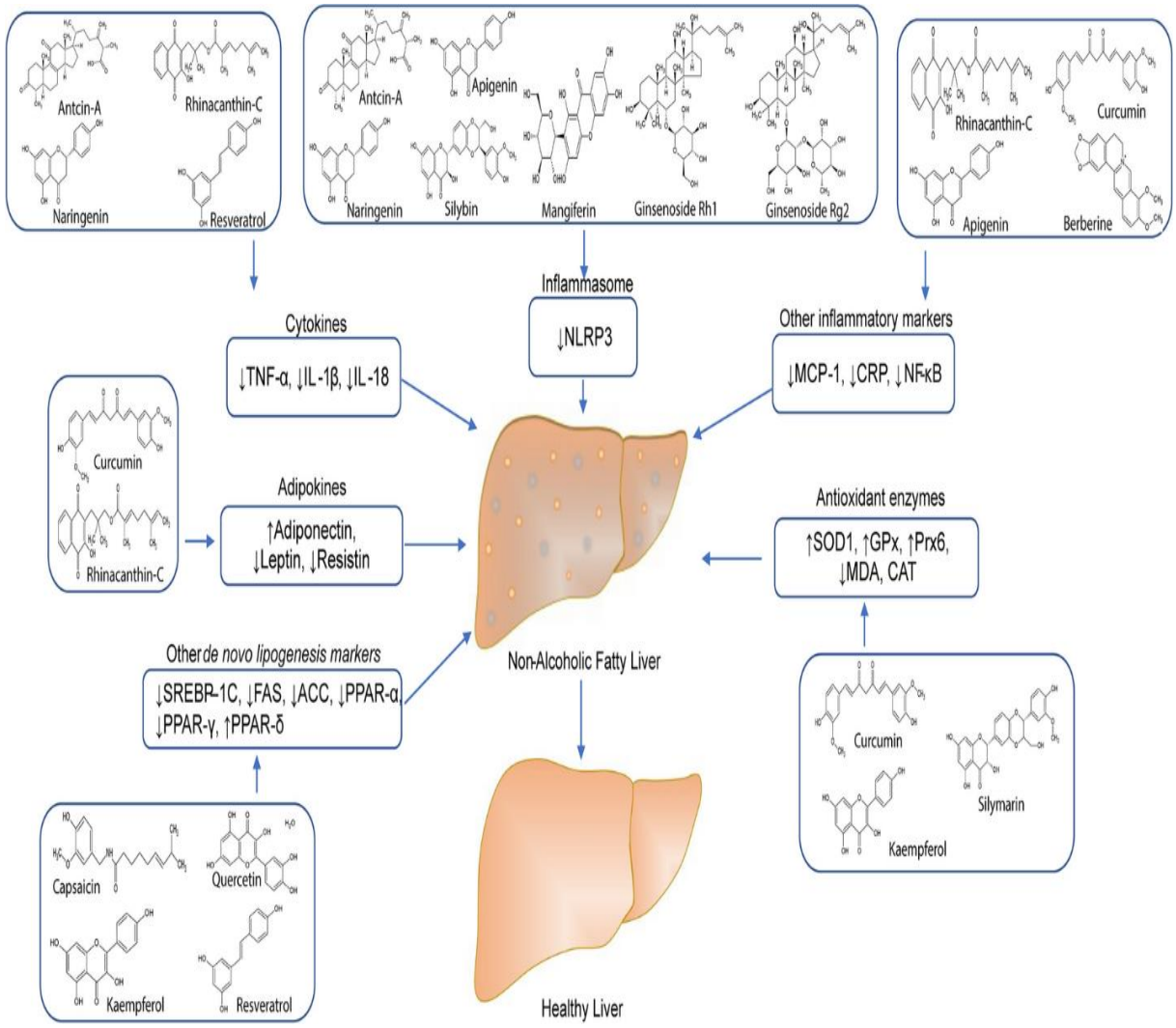

Figure 7: Mechanism of action of various bioactive phyto-constituents against NAFLD (Adapted from Pervej Alom Barbhuiya et al. [31])

5.3. Flavonoids

Polyphenolic chemicals called flavonoids are widely distributed in the natural world. They are often bound to sugars (glycosides) and are secondary metabolites in plants. Another form of flavonoids is aglycones, which lack a sugar group. Three rings make up the majority of flavonoids: one heterocyclic ring (C) and two aromatic rings (A and B). Subclasses of flavonoids are distinguished by differences in the C ring. Flavones, isoflavones, flavanols, flavanones, anthocyanidins, and chalcones are main subclasses (Figure 8) [32].

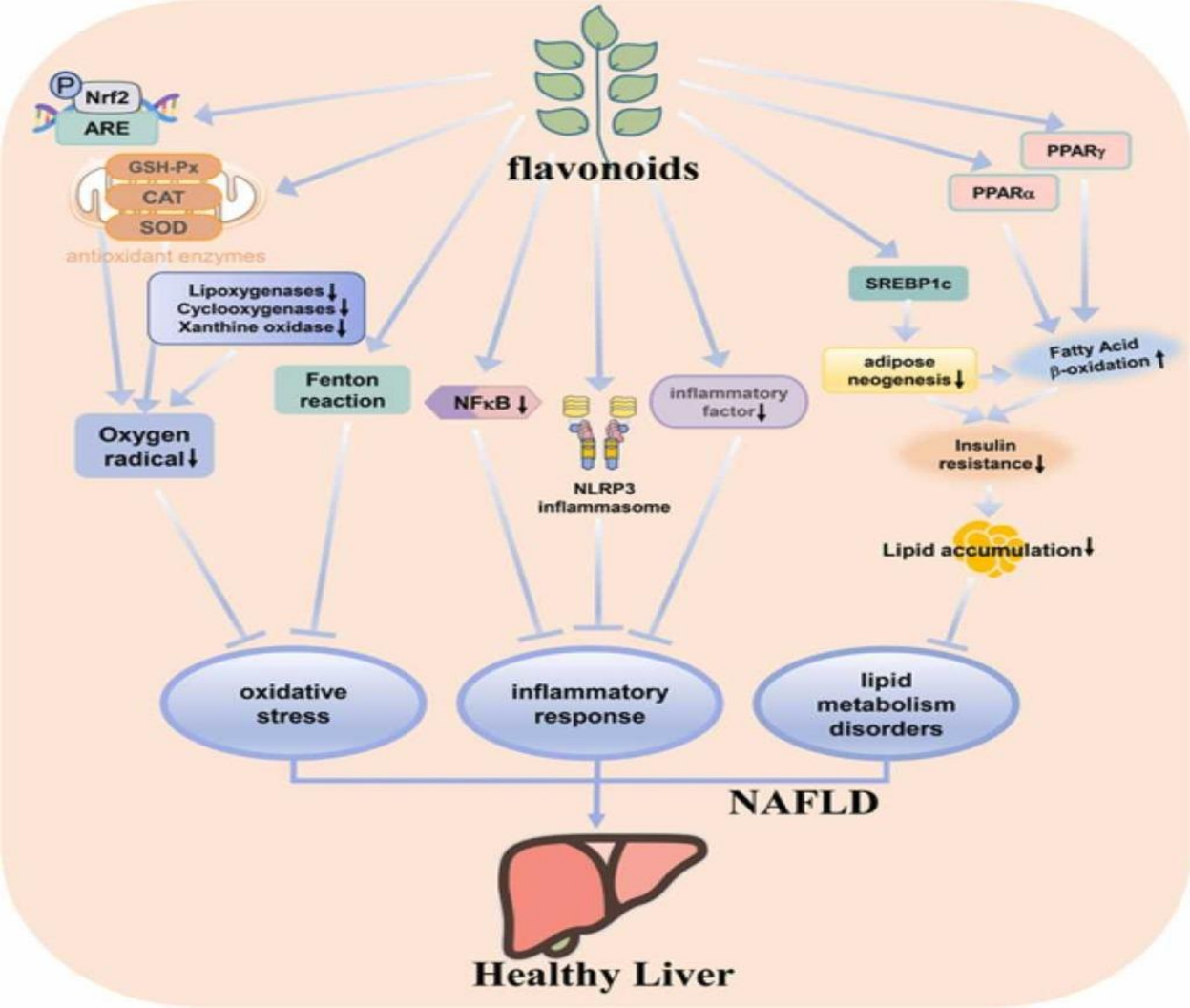

Figure 8: Flavonoids target the possible pathways in NAFLD (Adapted from Li et al. [32])

When it comes to treating NAFLD, flavonoids demonstrate the benefits of these bio-actives. These actions can be further classified as anti-inflammatory, antioxidant, or metabolic [33].

Figure 8 indicates that flavonoids function as both an antioxidant and an anti-inflammatory through a variety of pathways. Flavonoids have the ability to prevent the manufacturing of reactive oxygen species (ROS) and other active molecules, as well as shield antioxidant enzymes such as glutathione peroxidase (GPx) and inhibit enzymes that make ROS, such as xanthine oxidase. Furthermore, they are able to interact with the majority of antioxidant enzymes through Nrf2, the nuclear factor erythroid 2-related factor 2. By binding to antioxidant response elements (ARE), flavonoids enhance the transcription of ARE-driven genes, phosphorylate Nrf2, and cause Nrf2 to translocate into the nucleus, therefore mitigating oxidative stress-mediated damage. Furthermore, flavonoids have the power to chelate iron and other transition metals that stimulate the synthesis of free radicals, scavenging the free radicals produced by the Fenton reaction. Superoxide dismutase is sometimes referred to as catalase, KEAP1 (Kelch-like ECH-associated protein), L-glutathione, and GSH. Important inflammatory molecules from flavonoids in models of nonalcoholic fatty liver disease have been thoroughly studied, including NF-κB, NLRP3, iNOS, and COX-2. Flavonoids decrease the IKK complex and IκBa phosphorylation by reducing pro-inflammatory signals. This prevents the nuclear translocation of the NF-κB p65 subunit and the synthesis of inflammation producing genes. Flavonoids have the capacity to directly remove the expression or function of NLRP3, iNOS, and COX-2 in addition to their influence on the NF-κB-mediated regulation of these molecules' synthesis via several methods [32].

5.4. Terpenoids

Terpenoids are a family of naturally occurring active substances that may be used to treat a variety of illnesses because of their broad range of pharmacological activity and therapeutic advantages. Forty Three (43) terpenoids in total were identified as being used to treat NAFLD. Multiterpenoids, sesquiterpenoids,

diterpenoids, triterpenoids, and tetraterpenoids are the five categories of naturally occurring terpenoid compounds that were categorized based on structural similarities. By reducing insulin resistance, oxidative stress, inflammation, and problems with lipid metabolism, terpenoids have been shown to be beneficial in the treatment of non-alcoholic fatty liver disease (NAFLD). PPARs, Nrf-2, SIRT-1, and AMPK pathways are the main targets of terpenoid treatment. Terpenoids are a promising class of pharmaceuticals that may open up new avenues for NAFLD treatment [25].

Paeonia lactiflora Pall. contains a monoterpene glucoside called paeoniflorin, which has a range of pharmacological activity such as hepatoprotection, antioxidant, hypolipidemic, and hypoglycemic effects. Recent studies have shown that paeoniflorin, by increasing insulin signaling, promoting fatty acid oxidation, and inhibiting the liver's lipid synthesis, can ameliorate steatohepatitis caused by a high-fat diet. Pepidedoflorin significantly improved insulin sensitivity and serum lipid profiles, alleviated hepatic steatosis, and decreased blood insulin and glucagon levels in rats fed fructose. Moreover, paeoniflorin boosted the phosphorylation of AMP-activated protein kinase (AMPK) and protein kinase B (PKB/AKT) while decreasing the phosphorylation of acetyl coenzyme A carboxylase (ACC)1 in the liver. Furthermore, papeiniflorin enhanced the mRNA expression of hepatic carnitine palmitoyltransferase (CPT)-1 and protein expression, while decreasing the mRNA expression of fatty acid synthetase (FAS), stearyl coenzyme A decarboxylase (SCD)-1, and sterol regulatory element-binding protein (SREBP)1c. Insulin resistance and hepatic steatosis were improved as a result of the suppression of lipogenesis and the stimulation of β-oxidation and glycogenesis [34].

A naturally occurring pentacyclic triterpenoid carboxylic acid, ursolic acid (UA) is found in a wide range of herbs and plants. To prevent hepatic lipid buildup, dyslipidemia, and insulin resistance, UA may both promote lipid β-oxidation and reduce endoplasmic reticulum (ER) stress. A well-known member of the short leucine-rich proteoglycan (SLRP) family, DCN offers several therapeutic benefits,

such as the capacity to lessen tumor growth, fibrogenesis, and inflammation. An important component of both the extracellular and intracellular matrix is DCN. By modifying a number of signaling pathways, including TGF-β, insulin-like growth factor I receptor (IGF-IR), and hypoxia inducible factor 1 (HIF-1), it contributes to a number of cellular functions. Recent experimental research has shown a direct correlation between low glucose tolerance in obese mice and a lack of DCN, indicating a significant involvement in metabolic dysfunction. Additionally, DCN may be regulated by UA to treat NASH via the IGF-IR and HIF-1 signaling pathways, which would be beneficial for application and widespread adoption [35].

5.5. Other compounds

Glucosidates are secondary metabolites that include sulfur and are generated from cruciferous vegetables. Their strong antioxidant properties indicate that they may have anti-NAFLD properties. The glucosinolate present in broccoli, called glucoraphanin, is the precursor to sulforaphane. After 14 weeks of a 0.3% glucoraphanin supplementation, HFD-fed mice showed reduced hepatic steatosis and increased insulin sensitivity and glucose tolerance thanks to the activation of Nrf2. In addition, daily administration of ten mg per kg sulforaphane for eight weeks can lower insulin resistance in hyperlipidemic rats via inhibiting JNK and activating the FGF21 signaling pathway [36].

Allyl-isothiocyanate (100 mg/kg/d for eight weeks) has the potential to significantly reduce the inflammatory response and the build-up of liver lipids in mice fed a HFD. Additionally, treatment with 20μmol/L for 24 hours decreased PA-induced lipid accumulation and inflammation in AML-12 cells by suppressing the Sirt1/AMPK and NF-κB signaling pathways. There is a lot of promise for treating and preventing metabolic diseases, even though the exact process is yet unknown. We believe that mitochondrial function may be crucial in this regard [36].

The List of phytochemicals used to treat NAFLD, their sources, functions and possible mechanisms are presented in Table 1.

Table 1: Phytochemicals used to treat NAFLD

Classification	Natural product	Function	Mechanism/target	References
Polyphenols (Non-flavonoids)	Resveratrol RSV	reduction of ROS and inflammation, and enhancement of mitochondrial biogenesis	eNOS/NO/cGMP pathway, Akt/Nrf2, JNK pathway	[28]
		Promoting β-oxidation and mitotic dynamics	FAS, p-AMPK, CPT1a, Sirt1, PPARγ, SREBP-1c	[19]
		Mitochondrial elevation	UCP2	[37]
	Punicalagin (PU)	decrease in ROS and rise in ATP generation	Nrf2/HO-1/NQO1 pathway, PGC-1a	[38]
		Promotion of mitochondrial biogenesis and recovery of MMP	Nrf2, PGC-1a, FAS, ACC1	[38]
	Procyanidins	Suppress Inflammation and oxidative stress	IL-1β, NLRP3, Caspase-1 H2O2, MDA, SOD, CAT, GSH and ROS	[18]
		Promotion of mitochondrial biogenesis	PGC-1a, NRF1, TFAM, Mfn1, Mfn2	[19]
	Helenalin (HCM)	MMP restoration and ROS decrease	Nrf2 pathway, NQO1, HO-1, NF-Kb	[32]
	Gastrodin	inhibits liver steatosis	AMPKa, Nrf2 pathway	[4]
	Caffeic acid	Anti-inflammatory Reduces lipid accumulation and production	FAS, AMPK pathway, SREBP1, FAS, GPAT, HMGCR	[4]
Flavonoids	Luteolin (Flavonol)	Reduce inflammation and lipid accumulation	pro-inflammatory pathways of IL-1 and IL-18, activation of LXR-SREBP-1c	[39]
	Naringenin (Flavonones)	reduce inflammation mitochondrial biogenesis	NF-κB pathway, AMPK activation, PGC-1a, TNF alpha	[40]
	Silibinin (Flavonolignans)	Anti-inflammatory reduce hepatic fat	SERBP-1c, NF-κB and TLR inhibition, AKT pathway	[32]
	Qucertin (Flavonol)	Anti-lipogenic, anti-inflammatory	Suppress SERBP, Acyl CoA carboxylase, NF-κB	[16]
	Rutin	Inhibit lipogenesis,	inhibits CD36 and SREBP-1c	[32, 41]

	(Flavonol)	anti-oxidant	while activating PPAR-a	
	Kaempferol	Anti-oxidant, inhibit lipogenesis, anti-inflammatory	SREBP1, FAS, SOD-1	[16, 42]
	Genistein (Iso-flavonoids)	Antioxidant, anti-inflammatory, anti-fibrotic	SREBP-1c, FAS, NF-κB, and JNK are inhibited; PPARa is activated	[32]
	Vitexin	lipid metabolism modulation, anti-inflammation	inhibiting TLR4/NF-κB signaling, AMPK pathway	[43]
Alkaloids	Betaine	ameliorated hepatic steatosis	activation of AMPK, down-regulation of SREBP-1c, up-regulation of PPARa	[30]
	Berberine	fatty acid oxidation, preventing liver cells from synthesizing new lipids, ROS reduction	Activation of AMPK Nrf2, MRC complex	[30]
	Hirsutine	Ameliorating insulin resistance	PI3K	[36]
	Piperine	Inhibit lipid metabolism	Down regulation of PPAR, SREBP-1c, AMPK,	[30]
	Benzoyl aconitine (BAC)	mitochondrial biogenesis and the stimulation of mitophagy	AMPK pathway, NDUFS1, SDHA, UQCRC1, COX4, ATP5A1	[19]
Terpenoids	Paeoniflorin (Mono-terpenoid)	Regulates lipid metabolism	Insulin signaling pathway, AMPK pathway, FAS	[34]
	Geraniol (Mono-terpenoid)	prevent hepatic fat buildup, inflammation, apoptosis, fibrosis, and oxidative stress	Not discovered yet	[25]
	Carnosic acid (Di-terpenoid)	Inhibit IR and lipid accumulation, anti-inflammatory,	the PI3K/AKT and NLRP3 signalling	[25]
	Dehydroabietic acid (Di-terpenoid)	Reduced blood lipid	Keap1/Nrf2-ARE signaling pathway activation	[25]
	Ursolic acid (Tri-terpenoid)	Anti-inflammatory, anti-oxidants	PPAR-a, TGF-β, IGF-IR	[16, 35]
	Glycyrrhizic acid (Tri-terpenoid)	Reduce inflammation and lipogenesis	Inhibit FAS pathway	[25]
	Mogroside V (Tri-terpenoid)	Inhibit lipid accumulation, ameliorated	Activate AMPK signaling pathway	[25]

		hepatic steatosis		
	Lutein (Tetra-terpenoid)	Decrease body weight and hepatic steatosis, improve IR	Activate the SIRT1/PPAR-a signaling pathway	[25]
	β-caryophyllene (Sesquiterpenoid)	Inhibit lipid accumulation, ameliorated hepatic steatosis	Activate AMPK signaling pathway	[25]
	Curcumol (Sesquiterpenoid)	Reduce inflammation, fibrosis, apoptosis, and improve liver function	Regulation of TLR4, TAK1, and NF-κB/P65	[25]
Other compounds	Polygonatum kingianum (PK) sulforaphane	Increase Mitochondrial biogenesis, anti-oxidants	CPT-1a, UCP-2, MRC complex, Nrf2 pathway	[19]
	Sulforaphane	Improving insulin resistance	JNK; FGF21	[36]

6. Conclusion

Fast increasing rates of NAFLD are associated with chronic liver disease, which is similar to the rise in obesity and metabolic syndrome. A multidisciplinary strategy with distinct risk categorization is necessary for management. Over the next ten years, there will be a major improvement in the therapy options for advanced illness stages. The FDA recommends physical exercise and dietary modification for treating NAFLD, but evidence suggests mitochondrial dysfunction is linked to the disease. Mitochondrial damage can exacerbate fibrosis, inflammatory processes, ROS generation, and lipid buildup. Natural remedies that control dynamics and modulate mitochondrial function can slow the progression of NAFLD. Chronic metabolic liver diseases like non-alcoholic fatty liver disease (NAFLD) can be effectively treated with alkaloids, flavonoids, phenolic compounds, and terpenoids such as berberine, 6-gingerol, 6-shogaol, NHP, celastrol, and amarogentin, as they have demonstrated therapeutic properties for creating functioning mitochondria and promote mitochondrial biogenesis. Combination therapy, which integrates pharmaceutical medicine with natural items, is a viable treatment for liver problems

connected to mitochondria. By enhancing mitochondrial homeostasis and optimizing the therapeutic benefits of natural products, this approach may be able to prevent NAFLD and other chronic liver illnesses. Developing compounds targeting mitochondria could provide new therapeutic approaches.

Author contribution

Conceptualization, A.M.U.; writing-original draft preparation, S.N. and A.M.U.; writing-review and editing, S.Q., F.AJ. M.T.R.

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Conflict of Interest

The authors declare no conflict of interest.

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PHARMACOLOGY AND THERAPEUTICS – INNOVATIVE AND APPLIED CONCEPTS

Review Based Book Chapter

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REVIEW BASED BOOK CHAPTER

PATHOPHYSIOLOGY AND TREATMENT APPROACHES FOR AMYOTROPHIC LATERAL SCLEROSIS (ALS): A NARRATIVE REVIEW

J. Narayanan[1*], R. Sridevi[1], V. Chitra[1], V. Manimaran[2], T. Tamilanban[1]

[1]Department of Pharmacology, SRM College of Pharmacy, SRM Institute of Science and Technology, Chennai, India

[2]Department of Pharmaceutics, SRM College of Pharmacy, SRM Institute of Science and Technology, Chennai, India

For Correspondence
narayanj@srmist.edu.in

Abstract

A complicated neurodegenerative disease, amyotrophic lateral sclerosis (ALS) mostly affects motor neurons, resulting in a gradual weakening and atrophy of muscles. This review focuses into the pathophysiology of amyotrophic lateral sclerosis (ALS), providing insight on the complex genetic and molecular pathways at work and the ways in which it overlaps with frontotemporal dementia. Oxidative stress, excitotoxicity, mitochondrial dysfunction, disruption of axonal transport, neuroinflammation, DNA damage, and poor protein homeostasis are key pathological characteristic features of amyotrophic lateral sclerosis (ALS). Important hereditary factors include mutations in genes such as SOD1, FUS, and C9ORF72. About 15% of amyotrophic lateral sclerosis (ALS) patients also show signs of frontotemporal dementia, in addition to the characteristic motor symptoms and cognitive and behavioral abnormalities. The condition is characterized by aberrant TDP-43 or FUS protein aggregates, and the C9ORF72 gene mutation is the most prevalent genetic component. Physical therapy, dietary therapies, and respiratory support are all parts of the multidisciplinary care that is currently available to patients in an effort to reduce symptoms and enhance their quality of life. Gene therapies and novel pharmacological medicines that target specific disease pathways are among the novel treatments being researched. In order to address the complex nature of amyotrophic lateral sclerosis (ALS) and enhance patient outcomes, the field is shifting towards early intervention techniques and personalized medication.

Keywords
Amyotrophic Lateral Sclerosis (ALS), Frontotemporal Dementia, C9ORF72 Gene, Neuroinflammation, ALS Therapy

Introduction

A form of motor neuron disease that often manifests in adults, amyotrophic lateral sclerosis, is often called a neuromuscular complaint due to the fact that its symptoms are characterized by a reduction in muscle strength and size. The medical community has been under pressure due to advancements within the last two decades in the fields of clinical, genetic, and molecular biology. Similar to ALS with regard to cognitive, behavioural, and motor impairment, frontotemporal dementia is a unique kind of neurodegenerative illness. Fifteen percent of ALS patients exhibit frontotemporal dementia, while the remainder patients have varied levels of dysfunction in thinking or acting [1]. But in primary progressive aphasia (18%) and behavioural variant frontotemporal dementia (15%), ALS is present [2, 3]. In the cerebral cortex, inappropriate aggregates of transcription factor 43 (TDP-43) or fused in sarcoma (FUS) form in the cytoplasm of neurons. In individuals of European heritage, this can result in frontotemporal dementia, ALS, or both [4-6]. C9ORF72 is the most common gene involved in this process. Thus, amyotrophic lateral sclerosis (ALS) is commonly perceived as a complex neurodegenerative disease that falls within the spectrum of frontotemporal dementia-motor neuron disease (MND) [7, 8]. The recent development of amyotrophic lateral sclerosis (ALS) among this group of disorders has provided new possibilities for investigating the pathophysiology of the disease and developing novel therapeutic strategies.

Loss of both lower and higher motor neurons, alterations in muscle denervation, and degeneration of the corticobulbar/corticospinal pathways are the main symptoms of ALS. TDP-43 proteinopathy is involved in around 97% of cases of ALS, where TDP-43 forms cytoplasmic clumps after mislocalizing from the nucleus [9-11]. On the other hand, it is due to mutations in the cu-Zn superoxide dismutase 1 (SOD1) or FUS proteins exhibits distinct cytoplasmic protein aggregation and does not contain TDP-43 [12-15]. The most common genetic variant is characterized by excess p62-positive aggregates from dipeptide repeat proteins (DPRs) and TDP-43 mislocalization. These are linked to hexanucleotide expansions in C9orf72 [16].

A battery of blood tests, spine and brain imaging to eliminate out structural pathology, and a neurophysiological evaluation are among the diagnostic procedures that are ruled out due to mimic disorders of ALS [17]. For the diagnosis of ALS, the updated. The criteria of El Escorial [18], AWAJI Shima's specifications [19], in addition to the streamlined Gold Coast norms [20] were added. An ALS-prone patient is most affected by neuromuscular respiratory failure produced on by non-invasive ventilation [21, 22].

Enhancing the dosage used to cure ALS is the goal of cellular therapy [23]. By energy conservation and stretching exercises, physical therapy assists with problematic symptoms of ALS, such as fatigue and muscle stiffness [24]. It has been demonstrated that PT drastically improves an ALS patient's quality of life [25]. Various physical, psychological, and cognitive difficulties are faced by people with ALS, which can make it challenging to provide each aspect of their care. More research is needed to create nonpharmacological treatments for ALS that could lessen the emotional impact that the disease has on patients and those who care for them [26].

Epidemiology

Worldwide, ALS probability and occurrence were determined to be 4.42 and 1.59 per 100,000 people, respectively. Geographically, south Asia has the lowest and western Europe the highest. The incidence of ALS increases year by 0.00013, and more males than women are affected [27, 28].

PATHOPHYSIOLOGY

Genetic Makeup

In 1993, familial ALS (fALS) was estimated to be caused by SOD1 mutations in 10–21% of ALS patients. As of right now, 60–70% of cases are identified as fALS [29]. However, ALS is usually brought on by a combination of hereditary and environmental factors in 90–95% of cases. Genetic factors can cause ALS even in individuals without a family history, but the majority of cases (90–95%) are sporadic and have an estimated 50% heritability [30]. Genome-wide association studies have revealed that rare alterations have a significant role in shaping the molecular structure of ALS. The categorization of ALS has evolved from simple fALS and sALS to an enhanced complex risk gene-based molecular sub

classification [31]. Nearly thirty genes have been linked to ALS. In European families, a significant portion of cases, around 70%, are familial and have connections to FUS, C9ORF72, SOD1, and TARDBP. A recent study has uncovered 15 previously unknown risk loci [32], emphasizing the fact that ALS risk and disease severity are genetically independent. Neuroinflammation, mitochondrial dysfunction, and oxidative stress play crucial roles in physiological mechanisms. Every ALS patient has experienced positive outcomes from thorough genetic screening, as 21% of them have shown harmful mutations that can be clinically reported, while another 21% have variations of unclear significance [32, 33]. Genetic profiling has the potential to replace the outdated classifications of fALS and sALS, leading to advancements in therapy development and drug screening. The age of onset can vary even among members of the same family who have the same genetic mutation; in some cases, the mutation can exist for over 50 years prior to the beginning of disease. This indicates more than one process influenced due to a mixture of hereditary, behavioural, and ecological variables [34].

Oxidative Stress

Presently, significant existing research suggesting that vital significance of oxidative damage within the development of ALS, along with the compromised ability to defend against oxidative stress in the disease. This involves disrupting the cytoprotective system mediated by the antioxidant response element (ARE) on nuclear factor erythroid 2-related factor 2 (Nrf2), as well as glutathione homeostasis [35-40]. It has been demonstrated that both human ALS specimens and models of the illness exhibit changed oxidative stress biomarker profiles [41]. Aggregates of acetylated TDP-43 are enhanced by biochemical and cell-based methods, even though acetylation of TDP-43 prevents RNA binding and encourages the formation of hyperphosphorylated TDP-43 species, which are comparable to the harmful inclusions observed in the central nervous systems of ALS patients and in human ALS bio samples [42]. The phosphorylation of TDP-43 by GADD34 is enhanced by prolonged oxidative stress [43]. When TDP-43 aggregates in the cytoplasm, mitochondrial function is dysregulated [44]. Oxidative stress plays a role in the interaction between nearby astrocytes, microglia, and motor neurons [45, 46]. In a specific case, data suggests that astrocytes upregulate the

antiporter for cysteine and glutamate in reaction to elevated oxidative stress, which releases glutamate and can result in motor neuron excitotoxicity [47, 48].

Excitotoxicity

In ALS, excitotoxicity is caused by excessive postsynaptic glutamate receptor activation [49]. Prolonged elevation of glutamate at synapses in motor neuron excitotoxicity activation, increases amounts of calcium within cells, and inhibits the glutamate–cysteine antiporter, which lowers cysteine absorption. Long-term pathological alterations carried on by excitotoxicity include mitochondrial calcium excessive and ER stress [50-52]. In motor neurons that are affected by ALS, excitotoxic damage is more likely to occur because of decreased the expression of proteins that buffer calcium and increased expression of calcium-permeable AMPA receptors [53]. Metabolic glutamate receptors are becoming new potential therapeutic targets in ALS because of the possibility that their control will both reduce glutamate release and stimulate neurotrophic factor synthesis (NTFs).

Mitochondrial Dysfunction

Patient biosamples and ALS model systems describe disruptions to the mitochondria (axonal transport, structure, and dynamics), excessive production of ROS and decrease in ATP, disruption of calcium buffering, and induction of apoptosis [54, 55]. Several pathways have established a connection between mitochondrial dysfunction and mutations in certain amyotrophic lateral sclerosis (ALS) genes [56]. Numerous medications that target reactive oxygen species (ROS) and/or mitochondrial function, including creatine, coenzyme Q10, dexpramipexole, olesoxime, and dexpramipexole, performed well in animal models used for research but failed human trials [57].

Impaired Protein Homeostasis

Protein synthesis and degradation remain in control by a complex network that reacts to stress signals. This network includes the cytosolic heat shock response, unfolded protein responses in the endoplasmic reticulum (ER), and mitochondria [58]. Protein aggregates and a compromised proteome are hallmarks of age-related neurodegenerative disorders including spinal cord injury (the condition). Dysfunctional

proteostasis is a key component in the pathogenesis of amyotrophic lateral sclerosis (ALS), and several proteins associated with the disease either directly or indirectly control proteostasis [58-60]. Specifically, maturation is regulated by ubiquilin 2, alsin, FIG4, VCP, and CHMP2B, whereas autophagy initiation is dependent on ubiquilin 2, optineurin, sequestosome 1/P62, and C9ORF72 [61]. Motor neurons are particularly vulnerable to proteome stress due to their large size, minimal heat shock response, and restricted expression of ubiquitin proteasome genes. One of the main characteristics of ALS is intracellular protein aggregates, particularly TDP-43 mislocalization, which causes abnormal splicing, increases DNA damage, changes the transcriptome, and impairs axonal translation [62, 63]. UNC13A mRNA has cryptic exon inclusion due to TDP-43 loss from the nucleus, which lowers UNC13A protein expression and may have an impact on vesicle development and neurotransmitter release [64, 65].

Neuroinflammation and Glial Contribution

Inflammation of the nervous system or brain pathogen-induced cause of the preclinical stage of ALS [66]. Astrocytes control inflammatory signalling and maintain the integrity of the blood-brain barrier by the production of either pro- or anti-inflammatory cytokines, such as prostaglandin E2 and transforming growth factor (TGF)-β [67-69]. Motor neurons cocultured with astrocytes generated from fibroblasts from ALS patients are hazardous to them [70]. The specific ways this toxicity occurs are still unknown, however decreased bioenergetic support due to lactate release and activation of the pro-nerve growth factor-p75 receptor are possible causes [71]. One major process of neuroinflammation in amyotrophic lateral sclerosis (ALS) is the activation of the microglial NLRP3 inflammasome. Regarding its possible use as a therapeutic target, NLRP3 inhibition has one that potential to decrease microglia-induced neuroinflammation and halt the progression of amyotrophic lateral sclerosis (ALS). The NF-κB protein is a master regulator of inflammation in persons with amyotrophic lateral sclerosis (ALS), according to recent discoveries [72].

DNA Damage and Repair

Oxidized deoxyguanosine (OdG) levels are greater in neurons and other postmitotic cells in central nervous system (CNS) tissues and biofluids from amyotrophic lateral

sclerosis (ALS) patients [73, 74]. New research has connected amyotrophic lateral sclerosis (ALS) to DNA damage response (DDR) activation and an increase in apurinic/apyrimidinic DNA sites, which are areas where DNA bases are damaged [75].

Impaired Axonal Transport and Integrity

In many models of amyotrophic lateral sclerosis (ALS) and across human patients, pathological buildups of organelles and phosphorylated neurofilaments within the terminals of motor neurons have been associated to defects in axonal transport [76]. New evidence suggests that amyotrophic lateral sclerosis (ALS) is the result of genetic mutations ANXA11 (a protein that hinders axonal RNA transport) and KIF5A (a protein that encodes a microtubule motor) [77, 78]. In SOD1-mutant rats, P38 MAPK inhibitors reverted back normal axonal transport, but in a targeted manner, IGF1R inhibitors improved the axonal transport of signalling endosomes. The presence of signalling endosomes in retrograde axonal transit is essential for maintaining axonal integrity [79, 80].

Advances in ALS Therapy

Multidisciplinary Care

American amyotrophic lateral sclerosis (ALS) patients may see a multidisciplinary team of healthcare professionals during a single clinic visit, including a pulmonologist, a speech-a social worker, a dietitian, a linguist, a physiotherapist, an occupational therapist, and an ALS specialist. An integrative strategy is used in the treatment of ALS. Connections to ALS/MND groups are made in order to obtain further assistance [81, 82].

Modulators of Disease

Excitotoxicity, oxidative stress, mitochondrial dysfunction, protein homeostasis, neuroinflammation, cell death, cytoskeletal integrity, axonal transport, DNA repair, RNA metabolism, and stress granule modulation have been the primary areas of emphasis for ALS therapy in the last 20 years [83, 84]. To ensure the effective development of ALS therapy, the worldwide ALS community must prioritize future initiatives such as improving data exchange, endpoint harmonization, and trial design and analysis and ensuring

equity of access. A treatment for amyotrophic lateral sclerosis (ALS) has been approved by the US Food and Drug Administration (FDA): a combination of sodium phenylbutyrate and taurursodiol. This medication targets mitochondrial malfunction, endoplasmic reticulum stress, and cell death [85]. Other approved medications include riluzole, an anti-glutamine medication [86], and edaravone, which decreases oxidative stress [87] does not have European approval with the purpose of addressing amyotrophic lateral sclerosis [88, 89].

Pulmonary Intervention

As mentioned earlier, the main cause of death for ALS patients is respiratory failure. For the treatment of amyotrophic lateral sclerosis (ALS), it is essential to do pulmonary tests such as spirometry, polysomnography, transdiaphragmatic pressure, sniff nasal pressure, arterial blood gas, and nocturnal pulse oximetry. Regular evaluations are crucial for spotting respiratory muscle weakness and facilitating early non-invasive ventilation intervention, both of which can improve survival and quality of life. Even though there isn't much thorough research on the advantages of mechanical insufflation-exsufflation, it's commonly used to help people cough and clear their airways. Research on integrating respiratory muscle training with swallowing exercises to improve coughing and swallowing is still ongoing [90, 91].

Diet and Nutritional Intervention

Reduction in ALSFRS-R scores is associated with a decrease in body mass [92]. Losing weight is complicated and associated with several problems, such as fatigue, hyper metabolism, dysphagia, reduced meal intake, and impaired dexterity of the limbs when using utensils [21]. A shorter survival time was linked to body mass index extremes (<18, >40), while the 30-35 body mass index range showed the best survival [93]. Most agrees that antioxidants, fruits, fiber, and carotenes should be included in the diet [94]. According to clinical guidelines, patients who have symptomatic dysphagia, prolonged feeding times, severe weight loss (more than 5–10%), and, in some situations, deteriorating respiratory function, should be evaluated for gastrostomy tube placement. Proper treatment, procedure scheduling, and patient selection are critical to the success of a gastrostomy. An excellent resource for ALS patients, caregivers, and

doctors, the Simplifying ALS initiative (www.alsuntangled.com) has evaluated the data for numerous dietary supplements and vitamins. Nevertheless, the majority of clinical trials have not shown a lower incidence of ALS progression [95, 96]. Studies have shown that vitamin E may protect against amyotrophic lateral sclerosis (ALS), and a recent phase 3 experiment found that treating patients with an ultrahigh dose of methylcobalamin (50 mg) somewhat slowed their clinical deterioration compared to placebo [56, 97, 98].

Emerging Treatments

An increase in ALS research treatments has occurred due to the ineffectiveness of FDA-approved drugs. The ALS platform trial makes use of a centralized infrastructure and a shared master protocol, enabling the simultaneous evaluation of several agents [99]. At least fifty tiny compounds are being studied for various uses. The FDA-approved medication tofersen (2023) has demonstrated efficacy in treating pathogenic gene expression in SOD1-ALS patients. Phase 1 studies are being conducted on gene therapy vectors that use adeno-associated viruses to reduce SOD1 levels, while phase 1-2 trials are now being conducted on antisense oligonucleotides that target C9ORF72 and FUS. Phase 2 trials are also evaluating monoclonal antibodies that target misfolded proteins.

Conclusion

Over the past twenty years, we have seen a significant advancement in basic ALS research. But one of the main reasons for patient and caregiver frustration is the absence of substantial progress in converting this amount of knowledge into practical treatments. By consolidating biomarkers, developing systematic and innovative clinical trials, and concentrating on early disease among carriers of pre-symptomatic gene mutations, the discipline is drawing nearer to translating fundamental scientific discoveries into treatments that affect disease. As with cancer therapeutics, the hope is that the larger population of people living with sporadic amyotrophic lateral sclerosis (ALS) can find a personalized solution that limits disability and allows them to live with dignity by identifying risk gene variants and finding ways to identify the dominant mechanism (e.g., pathogenic inflammation, activation of retro-transposons, and oxidative stress) serving as the agent responsible for spreading some diseases.

Conflicts of Interest

The authors declared no conflict of interest.

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