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Carvedilol: New pharmacological approaches

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ABSTRACT

Carvedilol is a non-selective β-blocker with α1-blocking properties which is widely prescribed for treating hypertension, heart failure, and left ventricular dysfunction following myocardial infarction. It has a unique pharmacological profile and acts by several mechanisms of action, making it particularly effective in cardiovascular disorders therapy. Carvedilol exhibits antioxidant properties by scavenging reactive oxygen species (ROS) and reducing oxidative stress. Moreover, it has anti-inflammatory effects by reducing the levels of pro-inflammatory cytokines. Furthermore, it exhibits antiapoptotic properties, which play a crucial role in its therapeutic effects. By mitigating ROS, carvedilol helps to preserve mitochondrial function and prevent the release of pro-apoptotic factors which would otherwise initiate the cell death cascade. Additionally, carvedilol modulates signaling pathways that influence apoptosis. Overall, the combination of adrenergic-blocking, antioxidant, antiapoptotic, and anti-inflammatory properties makes carvedilol a multifaceted drug with significant therapeutic benefits. In our lab, we investigated new pharmacological actions of carvedilol in different experimental models. Therefore, this review aims to illustrate our new findings in addition to other labs' findings in a comprehensive way to be helpful to readers interested in this field. These studies involved in vitro and in vivo experiments using cellular and animal models, which have paved the way for clinical investigation of carvedilol in the management of distinct types of diseases.

1. Introduction

Carvedilol"1-(9H-carbazol-4-yloxy)-3-[2-(2-methoxy phenoxy)ethylamino]propan-2-ol" (Figure 1) is a third-generation vasodilatory antihypertensive agent. It was licensed in USA as a prescription medicine in 1995 after being patented in 1978 [2]. Carvedilol is a racemic mixture in which the S (-) enantiomer contributes to nonselective β-adrenoreceptor blocking activity whilst the potency of α1-adrenergic blocking action is equal in both S(-) and R(+) enantiomers [3]. Likewise, it is considered as a β-arrestin biased-agonist [4]. Moreover, former studies from our lab and other labs revealed calcium channels blocking, antioxidant, antiproliferative, anti-inflammatory, insulin-sensitizing, cardioprotective against dexamethasone-induced cardiotoxicity, hepato-protective against hepatic ischemia/reperfusion injury, and antiarrhythmic actions to be involved in its beneficial effects [5-11]. renoprotective against renal ischemia/ reperfusion injury and dexamethasone-induced nephrotoxicity,

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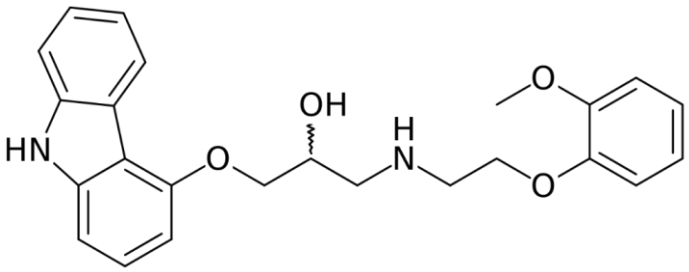

Figure 1: Chemical structure of carvedilol [1]

Notably, carvedilol differs from the other 3rd generation β-blockers, labetalol and nebivolol, in many aspects. Compared to labetalol, carvedilol has a more balanced ratio of α- to β- blockade, providing more consistent vasodilation and better blood pressure control. Additionally, carvedilol's antioxidant properties contribute to its cardioprotective effects, reducing oxidative stress and potentially improving outcomes in heart failure patients. In contrast, labetalol lacks these antioxidant benefits [12]. On the other hand, nebivolol has different pharmacological actions as it can selectively block β_1 adrenergic receptors without blocking either β_2 or α_1 adrenergic receptors. Moreover, unlike carvedilol, nebivolol can stimulate β_3 adrenergic receptors and nitric oxide production [13] (Table 1).

Table 1: Comparison of Carvedilol, Labetalol and Nebivolol

Feature	Carvedilol	Labetalol	Nebivolol
Drug class	Non-selective β-blocker and α_1 blocker (third generation beta blocker)	Non-selective β-blocker and α_1 blocker (third generation beta blocker)	Selective β_1 blocker with nitric oxide-mediated vasodilation (third generation beta blocker)
Mechanism of Action	Blocks β_1, β_2, and α_1 adrenergic receptors	Blocks β_1, β_2, and α_1 adrenergic receptors	Selectively blocks β_1 adrenergic receptors and enhances nitric oxide levels due to β_3 adrenergic receptor agonist activity
Cardioselectivity	Non-selective	Non-selective	β_1 selective
β_1/β_2-selectivity	0	+	+++
Lipophilicity	Moderate	Low	High
Peripheral Vasodilation	Yes (α_1 blocking effects)	Yes (α_1 blocking effects)	Yes (nitric oxide-mediated effects)
Use in Heart Failure	Yes (specifically indicated)	Off-label, less preferred	Off-label, less preferred

2. Pharmacological actions of Carvedilol

Carvedilol competitively blocks β_1-, β_2- and α_1-adrenoreceptors in a ratio of 10:10:1 [14]. Moreover, carvedilol is a β-arrestin biased-agonist that may contribute to multiple therapeutic actions [5]. In addition, some of the antioxidant effects of carvedilol and its metabolites include: preventing the depletion of body's natural antioxidant systems such as glutathione and vitamin E, scavenging detrimental free radicals, preventing lipid peroxidation in cardiac cell membranes and abolishing neutrophil release of O_2 [15]. Noteworthy, carvedilol enhances the tolerance to oral glucose uptake. These findings imply that α_1-adrenoceptor blockade, antioxidant activity and β-adrenoceptor blockade may have a greater positive impact on insulin sensitivity than β-adrenoceptor blockade alone, most likely because of the distinct effects on peripheral blood flow [16]. Moreover, carvedilol has favorable benefits on lipid metabolism. It prevents LDL oxidation, which lowers the amount of oxidatively modified LDL, a particularly hazardous and atherogenic substance for endothelial cells. Likewise, a drop in triglycerides and a rise in HDL cholesterol levels were observed in previous studies following carvedilol treatment [17, 18]. Interestingly, due to blocking of β-adrenoceptors, carvedilol suppresses the renin-angiotensin system (RAS), which

lowers the synthesis of angiotensin II [19]. As well, carvedilol administration is associated with balanced inhibition of calcium and potassium channels, diminishing of vascular smooth muscle cell proliferation and elevation of atrial natriuretic peptide (ANP) concentration in plasma [20].

3. Clinical uses

By virtue of carvedilol's balanced adrenoceptor blockade, antioxidant, antiarrhythmic, antiproliferative, antihypertrophic, antiatherogenic and anti-ischemic properties, it is indicated for the management of hypertension, ischemic heart disease (IHD) and mild to severe congestive heart failure (CHF). For patients with moderate to severe heart failure (left ventricular ejection fraction <40%) after acute myocardial infarction (MI), carvedilol (usually as an adjunct to ACE inhibitors, cardiac glycosides and diuretics) is prescribed to reduce the risk of hospitalization and recurrent heart attacks and enhance survival [21, 22]. Moreover, patients with mild to moderate cirrhosis have shown that carvedilol is effective in stopping bleeding from esophageal varices, and may also help to prevent further bleeding [23]. Furthermore, in patients with chronic stable angina pectoris, carvedilol decreases myocardial oxygen consumption and enhances exercise capacity when compared to placebo [24].

4. Experimental studies

4.1. On heart

4.1.1. Hypertension and Heart failure

4.1.1.1. Modulation of cardiac microRNAs

A study confirmed carvedilol's cardioprotection in H_2O_2-induced cell dysfunction and apoptosis in H9c2 cells that was attributed to altering the levels of circular RNA nuclear factor IX (circ_NFIX), microRNA-125b-5p (miR-125b-5p), and toll-like receptor 4 (TLR4) [25]. In the same context, carvedilol-induced downregulation of microRNA-1 targets heat shock protein 60 to prevent cardiac apoptosis [26].

4.1.1.2. Biased-agonism on β-arrestins

Noteworthy, in high-fructose, high-fat diet (HFrHFD)-fed mice and in streptozotocin (STZ) induced diabetes with deterioration of basal cardiac function model, long-term carvedilol administration ameliorated diabetic cardiomyopathy due to biased activation of β-arrestins that was decreased in diabetes [5, 27-29]. In the same context, by using the cardiomyocyte cell line H9c2, carvedilol activated βarrestin2-mediated Sarco(endo)plasmic reticulum Ca2+ATPase (SERCA)2a SUMO (small ubiquitin-like modifier)-ylation and activity via cardiac β_1-adrenoreceptors. This conferred the uniqueness for carvedilol use in the management of heart failure other than conventional β-blockers [30].

4.1.1.3. Amelioration of chemical- and drug-induced cardiotoxicity

Carvedilol can be used to mitigate cadmium induced cardiotoxicity in rats (as cadmium resulted in elevation of mean arterial pressure, cardiac enzymes, malondialdehyde (MDA), tumor necrosis factor alpha (TNF-α) and caspase-3 while reduction of heme oxygenase-1 (HO-1), nuclear factor erythroid 2-related factor 2 (Nrf2), endothelial nitric oxide synthase (eNOS) and total antioxidant capacity (TAC)) because of its capacity to reduce the associated hypertension in addition to its anti-inflammatory, anti-apoptotic, and antioxidant properties [31]. As well, carvedilol can mitigate doxorubicin-induced cardiotoxicity, trastuzumab-mediated left ventricular dysfunction, and dexamethasone-induced myocardial injury which has been found to be independent of its action on α1ARs [6, 32-34].

4.1.1.4. Modulation of cardiac β_1-adrenergic receptor crosstalk with nitric oxide and diacylglycerol pathways

Additionally, carvedilol stimulates cardiac inotropy by activation of β_1-adrenergic receptor and protein kinase G (PKG) and minimally enhances the amplitude of calcium waves. It is considered as a biased ligand to facilitate β_1-adrenergic receptor coupling to a G_i-PI3K-Akt-nitric oxide synthase 3 (NOS3) cascade and generates a strong β_1-adrenergic receptor-cGMP-PKG signal to enhance cardiac inotropy in the heart [35]. In a type 4 cardiorenal syndrome (CRS) rat model, carvedilol had better cardioprotective effects via attenuating cardiac apoptotic signaling pathways (caspase3/pS473 protein kinase B (Akt)) and modifying cardiac β_1-adrenergic receptor/β-

arrestin2/phosphatidyl inositol 4,5 bisphosphates (PIP2)/diacylglycerol (DAG) [36].

4.1.1.5. Impact on inflammatory cardiac disorders

In experimental autoimmune myocarditis, administration of carvedilol by gastric gavage for 3 weeks exerted cardioprotective effect that was associated with the inhibition of matrix metalloproteinase (MMP)-2 activity that is present in cardiomyocytes during oxidative stress and responsible for troponin and myofilament degradation and cardiac contraction impairment [37]. Another study confirmed this mechanism in acute ischemia-reperfusion heart injury model [38]. Also, it has been reported that carvedilol could modulate serum osteopontin (cardiac remodeling marker) and related inflammatory cytokine cascades that resulted in amelioration in cardiorenal functions in $Col4a3^{-/-}$ Alport mouse model of heart failure with preserved ejection fraction (HFpEF) [39]. Intriguingly, in collagen-induced arthritis (CIA) model in rodents, the sympathetic nervous system was hyperactivated because of proinflammatory cytokines (such as IL-6, TNF-α, and IL-1β) released from activated inflammatory immune cells. During rheumatoid arthritis, the activated local sympathetic neurons contributed to reduced cardiac performance owing to excessive release of adrenaline resulting in desensitization of β_1-adrenergic receptor in the heart. Therefore, carvedilol had substantial impact in the treatment of rheumatoid arthritis- induced heart failure [40].

4.1.2. Cardiac arrhythmia

It has been found that carvedilol was a negative gating modulator of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, which are crucial for the heart's spontaneous rhythmic action, via slowing down and shifting the voltage-dependent activation of the channel [41]. Moreover, carvedilol's blocking of voltage-gated K^+(Kv)1.3, Kv2.1 and human Kv4.3 channels expressed in HEK293 cells could be another possible reason for the not fully understood actions of carvedilol in various tissues especially in the relief of malignant ventricular arrhythmias [42-44]. Meanwhile, carvedilol has emerged as a treatment strategy for the prevention of digitalis-induced cardiac toxicity and arrhythmias because it was efficient in preventing ouabain-induced spontaneous contractions and apoptosis, through store overload-induced Ca^{2+} release (SOICR) process, suggestive of arrhythmogenic action without compromising inotropy [45]. In addition, without affecting the sarcoplasmic reticulum (SR) calcium load, carvedilol dramatically decreased the likelihood of spontaneous arrhythmogenic calcium waves. Based on its inhibitory effect on the SR calcium release channel, carvedilol appeared to have a significant anti-arrhythmic effect on atrial myocytes in male New Zealand White rabbits [46].

4.1.3. Ischemic heart disease

4.1.3.1. Modulation of cardiac microRNAs

In the mouse heart, carvedilol stimulated microRNA-125b-5p (miR-125b-5p) processing, which defended against acute myocardial infarction by suppressing pro-apoptotic genes bak1 (BCL2 antagonist/killer 1) and klf13 (Kruppel-like transcription factor 13) in cardiomyocytes that were elevated during dilated cardiomyopathy and cardiac ischemia, in addition to improving cardio-protection via β-arrestin-biased agonism of β_1-adrenergic receptor [47, 48].

4.1.3.2. Mitigation of vasospastic angina and atherosclerosis

Additionally, in A-kinase anchoring protein (AKAP) 150 knockout mice, by Ca^{2+} desensitization and inhibition of vascular smooth muscle cells (VSMCs) contraction through decreasing myosin light chain phosphorylation, carvedilol reduced coronary spasm without altering intracellular Ca^{2+}. Carvedilol's modification of calcium sensitization offered fresh perspective on the etiology and management of coronary spastic angina (CSA) [49]. Moreover, carvedilol may prevent atherosclerosis by increasing the expression of ATP-binding cassette transporter A1 (ABCA1), that acts as key reverse cholesterol transporter, and improving cholesterol efflux in exosomes and macrophages in Human hepatic (Huh-7) cells and Human monocytic cell line (THP-1), potentially via protein kinase B (Akt) and nuclear factor-κB (NF-κB) signaling [50]. Furthermore, in 20-week-old male apolipoprotein E-deficient C57BL/6 mice, carvedilol had the ability to prevent the expansion and monocyte chemoattractant protein-1 (MCP-1) elevation of angiotensin II-induced abdominal aortic aneurysm through its antioxidant,

atheroprotective and anti-inflammatory characters along with hemodynamic regulation [51].
It has been reported that carvedilol could improve left ventricular performance, lower oxidative stress and inflammation and relief myocardial hypertrophy leading to alleviation of post-infarction heart failure in rats [52]. Also, due to carvedilol's antioxidant action on cardiac mitochondria and blocking of β-adrenergic pathways, it could be a useful therapeutic intervention to inhibit cardiac postischemic dysfunction in hypothyroid rats [53]. In the same context, combined use of carvedilol and thyroid hormones may ameliorate cardiac dysfunction and mitigate the damage caused by oxidative stress after acute myocardial infarction through the Bax protein reduction, Akt activation, and β_1-adrenergic receptor blockade in male Wistar rats [54, 55]. Nevertheless, carvedilol inhibited vascular endothelial growth factor (VEGF) effects that was increased by hypoxia and eliminated the enhancing effects of adipose-derived stem cells (ASCs) on cardiac remodeling and dysfunction following myocardial infarction [56]. Noteworthy, carvedilol could modulate cardiac AMP-activated protein kinase (AMPK) signaling pathway to lessen the negative consequences of ischemia and reperfusion injury such as oxidative stress, endoplasmic reticulum stress, apoptosis and autophagy. Carvedilol resulted in significant increase in systolic left ventricular function, enhanced intrinsic left ventricular mechanics, improved metabolism, improved myocardial salvage and decreased infarct size in C57BL/6J mice [57]. Carvedilol's cardioprotective effects are summarized in figure 2.

4.2. On the liver

4.2.1. Hepatic toxicity and carcinoma

In doxorubicin/5-fluorouracil-induced hepatotoxicity model in female Wistar rats, carvedilol markedly reduced the serum levels of alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST). It also elevated the levels of hepatic catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) in addition to MDA reduction. These results showed potent hepatoprotective effects of carvedilol due to improve in vivo antioxidant actions [58]. In hepatic ischemia/reperfusion injury model in HFrHFD-fed mice, the hepato-protective effect of carvedilol was not dependent on the activation of either G protein-coupled receptor kinase 2 or 5 (GRK2 or GRK5) although GRK2 and GRK5 inhibitors elevated its anti-apoptotic, antioxidant and anti-inflammatory properties [7]. In the same context, another study reported that vasodilatory effect of carvedilol had a significant role in mitigation of nonalcoholic fatty liver in rats [59].

Furthermore, using human hepatocellular carcinoma (HepG2) cell lines, carvedilol induced over-expression of pro-apoptotic proteins (such as fas-associated protein with death domain (FADD), caspase-3, caspase-8) and down-regulation of anti-apoptotic and drug-resistant genes (such as mitogen activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK), protein kinase B (Akt), mechanistic target of rapamycin (mTOR), epidermal growth factor receptor (EGFR) and multidrug resistance genes-1 (MDR1)). Additionally, carvedilol protected non-tumor cells against oxidative stress and apoptosis through glutathione (GSH) elevation and MDA reduction [60].

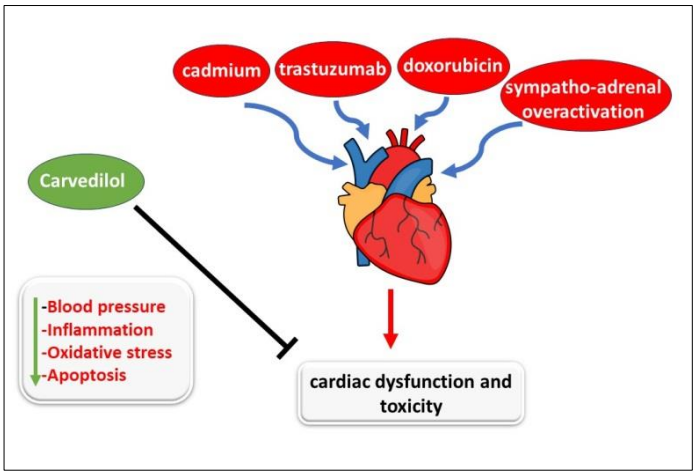

Figure 2: Amelioration of cardiac dysfunction and toxicity by carvedilol.

4.2.2. Liver fibrosis and cirrhosis

As carvedilol contributed to fibrotic nodules' reduction in the hepatic parenchyma, liver function enhancement, reduction in oxidative stress markers and downregulation of TLR4/PI3K/mTOR pathway in which TLR4 through MyD88 dependent pathway activated PI3K/AKT/mTOR pathway subsequently stimulating NF-κB activation and various inflammatory mediators release that resulted in hepatic damage and fibrosis, it was considered a potential

intervention for the regression of hepatic cirrhosis in a hamster model of CCl4-induced liver cirrhosis, paracetamol-induced acute hepatotoxicity in rats and leflunomide-induced liver injury in mice. In addition, cell proliferation markers, such as c-Myc (oncogene) and Ki-67 (indicator of immature liver cells), were slightly irregularly expressed in response to carvedilol [61-64].

Moreover, in cirrhotic rats, carvedilol reduced sinusoidal remodeling, portal pressure, gastric variceal bleeding and intrahepatic angiogenesis. In addition, carvedilol inhibited transforming growth factor β1 (TGF β1)-induced fibronectin synthesis in endothelial cells which involved in sinusoidal remodeling [65, 66]. Other investigations revealed that circulating microRNA-200a/SMAD7/TGF-β1/EMT/MAPK pathway (in which carvedilol improved the expression of anti-fibrotic miR-200a subsequently inducing protective SMAD7 that eventually inhibited pro-fibrogenic TGF-β1 as well as carvedilol inhibited α-SMA, vimentin (EMT markers) and NF-κB/MAPK that resulted in prevention of fibroblast production and collagen deposition), down-regulation of TLR4 expression and attenuation of hepatic stellate cell activation, proliferation, invasion and collagen synthesis through modulation of RhoA/Rho-kinase pathway were critical in the mitigation of hepatic fibrosis and cirrhosis by carvedilol [67-70].

4.2.3. Hepatic autophagy

Noteworthy, the rise in autophagosomes observed after carvedilol administration was not attributable to elevated autophagosome synthesis, but rather to compromised autophagosome destruction brought on by elevated lysosomal pH. Additionally, carvedilol impeded the autophagic flux and subsequently stimulated apoptosis in hepatic stellate cells, a new mechanism for carvedilol's attenuation of liver fibrosis [71]. Other studies in rats indicated that modulation of TLR-4/IL-6/TNF-α, COX-2 and eNOS/iNOS pathways (in which hepatic ischemia reperfusion contributed to TLR-4 signaling that induced NF-kB resulting in elevation of several inflammatory mediators such as interleukin-6, TNF-α and cyclooxygenase-II as well as it led to a marked reduction in eNOS (protective) but a significant rise in iNOS (pro-inflammatory) expression), targeting of dynamin-1-like protein (DNM1L), induction of nuclear receptor related-1 protein (Nurr-1)/glial cell line derived neurotrophic factor (GDNF)/AKT pathway (that had protective and antiapoptotic against hepatic ischemia reperfusion injury), suppression of apoptosis and the glycogen synthase kinase-3 beta (GSK3β)/NF-κB hub and promotion of autophagy and lysosomal biogenesis by carvedilol were responsible for its hepato-protective action [72-74]. Carvedilol's actions on hepatic autophagy are summarized in figure 3.

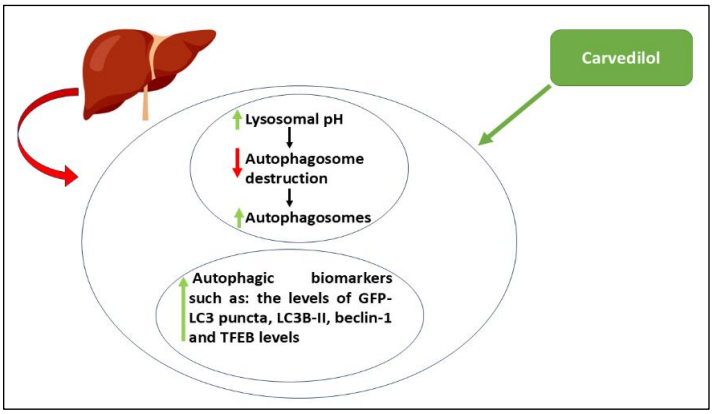

Figure 3: Effect of carvedilol on hepatic autophagy. GFP-LC3 (green fluorescent protein- light chain 3), LC3B-II (light chain 3B-II) and TFEB (transcription factor EB).

4.3. On the kidney

In HFrHFD-fed mice, it has been reported that renoprotective effect of carvedilol against renal-ischemia-reperfusion-injury (R-IRI) was dependent on lowering oxidative stress and inflammation without affecting lipid signaling [8]. In addition, carvedilol inhibited L-buthionine sulfoximine (BSO)-induced ferroptosis, the disruption of mitochondrial morphology and the mitochondrial ROS caused by ferroptosis inducers, so it could be used for acute kidney injury due to suppression of organ damage and scavenging of lipid peroxyl radical [75]. In other studies, carvedilol selectively blocked the organic cation transporters in renal proximal tubules limiting the renal accumulation of cisplatin and ameliorated cisplatin-induced nephrotoxicity via antioxidant activity or β-arrestin recruitment [76,77]. In dexamethasone-induced nephrotoxicity in rats, carvedilol markedly reduced the renal levels of Wnt3A/β-arrestin2/β-catenin pathway that involved in renal glomerular damage and proteinuria and this action had a role in its renoprotective effect [9].

4.4. On nervous system

4.4.1. Alzheimer's disease, Parkinson's disease and multiple sclerosis

In N2a/Swe.D9 mouse model in which Presenilin exon9 deletion mutant and Swedish amyloid precursor protein (Swe-APP) mutant was transfected into Neuro2a (N2a) cells, carvedilol inhibited apoptotic signals by lowering the amount of cleaved caspase-3 and cytochrome C release resulting in protection against endogenous β-amyloid (Aβ)-induced neurotoxicity and Alzheimer's disease [78]. Other investigations reported that R-carvedilol enantiomer (but not racemic carvedilol) relieved memory impairment, neuronal hyperactivity, and neuronal loss even in late stages of Alzheimer's disease (AD) via shortening ryanodine receptor 2 (RyR2) open time [79-81]. Also, in mouse hippocampus neurons, it has been reported that carvedilol activated the mutant β2-adrenergic receptor, promoting endogenous L-type calcium channel (LTCC) activity via cAMP/PKA signaling to control neuronal excitability in hippocampal neurons [82]. Surprisingly, in the rat hippocampal region, carvedilol reduced orchiectomy-induced emotional memory disruption and impairment [83].

In a Parkinson's disease rat model, rotenone-induced histological damage, motor impairments and problems with spatial memory were all alleviated with carvedilol.

Furthermore, carvedilol greatly prevented the rotenone-induced sub-expression of tyrosine hydroxylase (TH) in the rats' striata. Inhibition of rotenone-induced neuro-inflammation, microglial activation and glial fibrillary acidic protein (GFAP) release alongside with lessening in alpha-synuclein, phospho-Tau (P-Tau) protein expression and N-methyl-D-aspartate receptor activation were linked to these effects. Additionally, via inhibiting GSK3β and stimulating phosphoinositide 3-kinase (PI3K), carvedilol decreased the hyperphosphorylation of tau protein [84].

Furthermore, carvedilol had a neuroprotective action against experimental autoimmune encephalomyelitis (EAE)-induced multiple sclerosis through suppression of the TLR4/ myeloid differentiation factor 88 (MYD88)/tumor necrosis factor receptor-associated factor 6 (TRAF6)/c-Jun N terminal (JNK)/p38 mitogen-activated protein kinase (p38-MAPK) pathway [85]. In the same context, another study revealed the remyelinating action of carvedilol in cuprizone-induced rat model of demyelination [86]. These neuroprotective effects are summarized in figure 4.

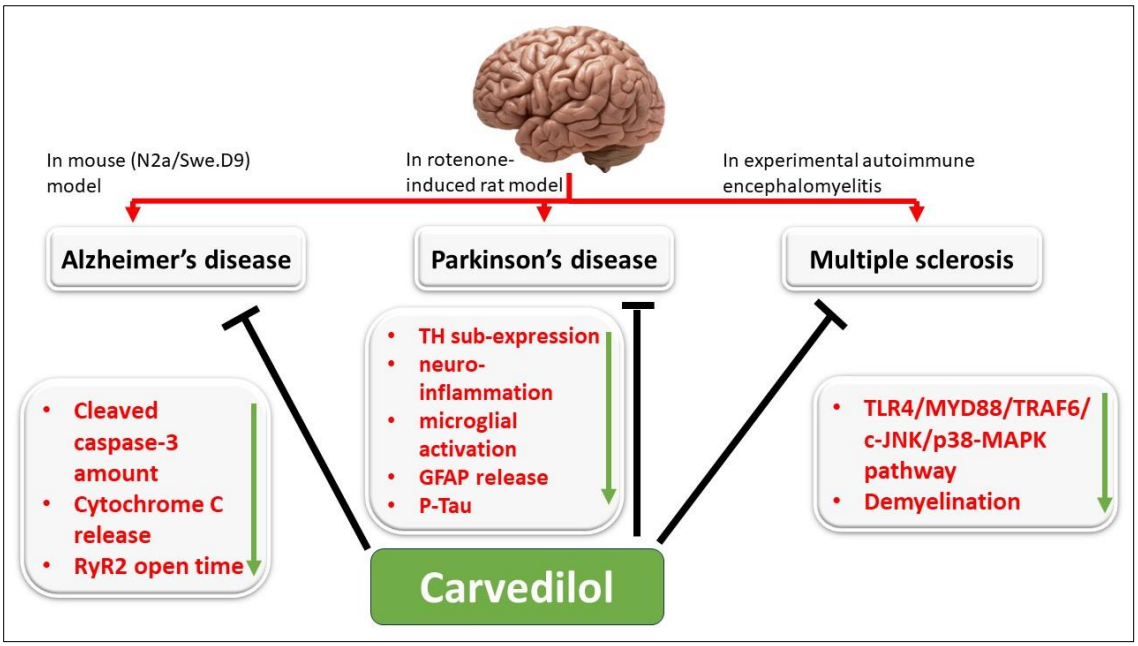

Figure 4: Mitigation of Alzheimer's disease, Parkinson's disease and multiple sclerosis by carvedilol. RyR2 (ryanodine receptor 2), TH (tyrosine hydroxylase), GFAP (glial fibrillary acidic protein), P-Tau (phospho-Tau), TLR4 (toll-like receptor 4), MYD88 (myeloid differentiation factor 88), TRAF6 (tumor necrosis factor receptor-associated factor 6), c-JNK (c-Jun N terminal) and p38-MAPK (p38 mitogen-activated protein kinase).

4.4.2. Depression and neurological damage

Through the use of network pharmacology analysis integration, carvedilol may have potential therapeutic benefits in the management of ischemic cerebrovascular disease (ICD) by modulating a number of interrelated biological mechanisms [87]. Another study suggested that carvedilol interacted with both in vitro and in vivo serotonin 2A receptors which could be a therapeutic option for some neurological or behavioral disorders [88].

In in vivo STZ-induced diabetic neuropathy and in vitro high glucose-induced neuronal damage, carvedilol could reduce nerve growth factor (NGF) content in the dorsal root ganglion (DRG) that possessed a sensitizing effect on nociceptors and had an antioxidant impact, which may account for some of its neuroprotective benefits [89, 90]. As well, it has been reported that carvedilol elevated brain concentrations of brain-derived neurotrophic factor (BDNF) that was reduced during depression and stress and had antidepressant properties in a mouse model of chronic unpredictable stress (CUS)-induced depression and due to its antioxidant and neurotrophic properties, it could enhance cognitive function and social behavior [91]. Other studies showed that the neuroprotective action of carvedilol against hepatic encephalopathy- and acrylamide- induced brain damage in mice was attributed to its regulation of inflammation, oxidative stress and apoptosis markers [92-93].

4.5. Antimicrobial experiments

Although, Gram-negative bacteria (such as E. coli and P. aeruginosa) demonstrated a significant level of resistance to carvedilol through its breakdown into metabolites, Gram-positive bacteria (such as S. aureus and S. epidermidis) revealed the most powerful carvedilol-induced suppression of bacterial growth through alterations in S. aureus's cellular membranes composition and permeability [94]. Another study revealed that carvedilol promoted the antimicrobial action of ciprofloxacin against S. aureus [95]. In the same context, it has been reported that carvedilol had antiparasitic effects against *Trypanosoma cruzi*, the causal agent of Chagas disease, as carvedilol promoted the production of immature autophagosomes, which were less hydrolytic and acidic. This activity led to a considerable decrease in infection and parasite burden by impairing trypomastigotes' survival as well as the replication of amastigotes and epimastigotes. Additionally, carvedilol decreased the peak of the whole-body parasite load in infected mice [96].

Likewise, carvedilol blocked the degradation of β-arrestin 2, which was induced by viral infection, so carvedilol may act as a potential antiviral drug candidate [97]. As well, carvedilol could fight coronavirus infectious disease 19 (COVID-19) via down-expression of angiotensin-converting enzyme 2 (ACE 2), SARS-Coronavirus-2 host receptor, reduction of interleukin 6 (IL-6) which played a major role in the inflammatory cascade of COVID-19 and inhibition of the main protease (Mpro) which was one of SARS-CoV-2 essential proteins [98-100].

4.6. On cancer

Unlike unbiased β-blockers, carvedilol is a powerful cancer preventive agent owing to preventing (or "hijacking") ERK translocation into the nucleus in the mouse epidermal JB6 P+ cells treated with the tumor promoter EGF model [101, 102]. Other reports suggested that inhibition of polymerase 1 and anti-apoptotic protein B-Cell Lymphoma 2 (Bcl-2) with carvedilol might be the reason for its cancer-preventive action [103, 104]. Noteworthy, chronic high dose of carvedilol inhibited bone sarcoma cell viability and clonogenic survival and elevated radiosensitivity in canine osteosarcoma cells [105]. Also, another study found that carvedilol inhibited the reactive oxygen species (ROS)-mediated phosphoinositide 3-kinase (PI3K)/ protein kinase B (AKT) signaling pathway and suppressed the malignant growth of mammary epithelial cells [106]. In murine epidermal JB6 P+ cells, the skin cancer chemo-preventive effects of carvedilol were dependent on DNA repair regulation [107]. Cancer preventive pathways by carvedilol are summarized in figure 5.

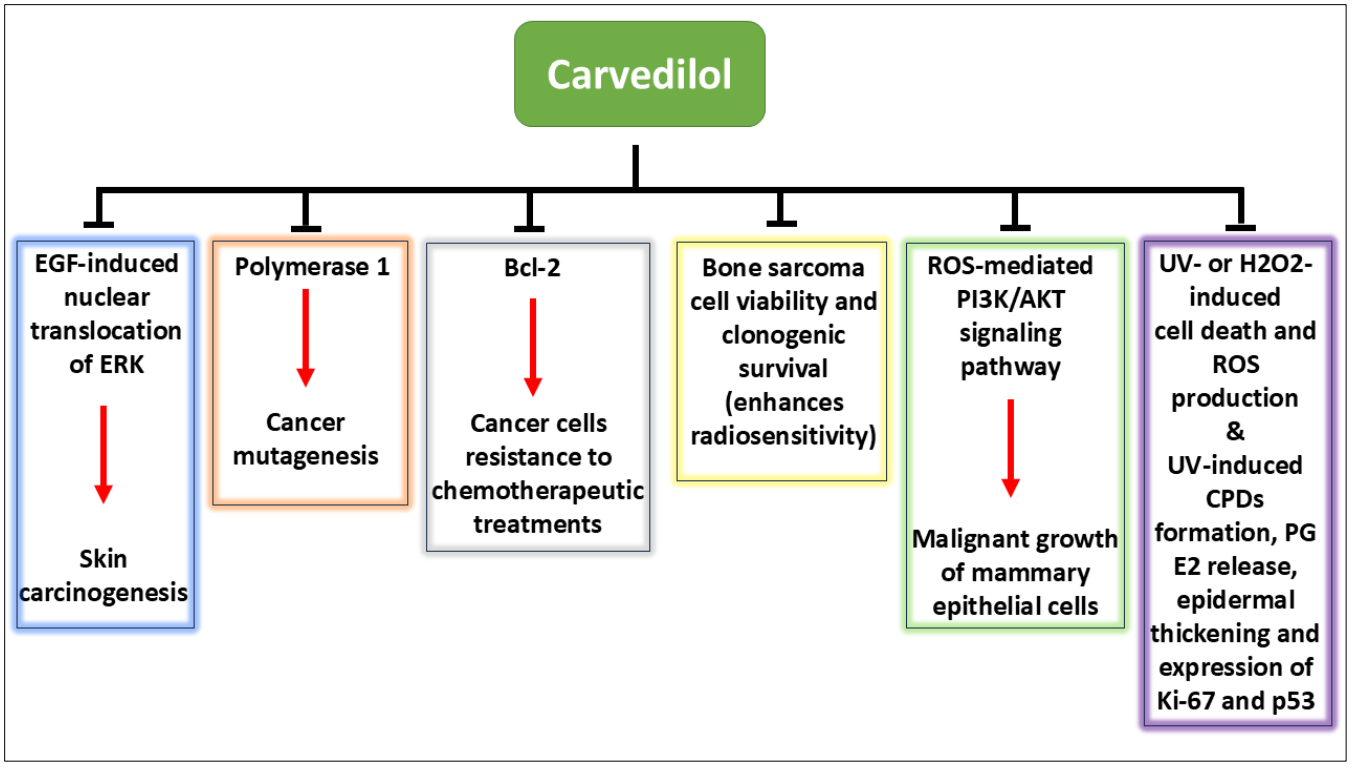

Figure 5: Cancer preventive pathways by carvedilol. EGF (epidermal growth factor), ERK (extracellular signal-regulated kinase), Bcl-2 (B-Cell Lymphoma 2), ROS (Reactive oxygen species), PI3K (phosphoinositide 3-kinase), AKT (protein kinase B), UV (ultraviolet), H2O2 (hydrogen peroxide), CPDs (cyclobutane pyrimidine dimers), PG E2 (Prostaglandin E2), Ki-67 (marker of proliferation Kiel 67) and p53 (transformation-related protein 53).

4.7. On skin

It has been documented that carvedilol could mitigate nitrogen mustard–induced skin injury [108]. By blocking cAMP/protein kinase A/ phosphor-cAMP response element-binding protein (CREB) signaling, carvedilol efficiently reduced melanogenesis in human melanocytes and ex vivo human skin [109]. In the rosacea-like inflammation mouse model, through inhibiting the Toll-like receptor 2 (TLR2)/ kallikrein 5 (KLK5)/cathelicidin pathway in macrophages, carvedilol could mitigate the skin inflammatory response associated with rosacea [110].

4.8. On inflammation

In a mouse model of nucleotide oligomerization domain (NOD)-like receptor family pyrin domain containing-3 (NLRP3)-associated peritonitis, carvedilol was considered an autophagy inducer as it suppressed the pyroptosis and activation of NLRP3 inflammasome, ASC oligomerization and the lysosomal and mitochondrial damage [111]. It has been reported that particularly in the dental pulp's deeper areas, carvedilol gel might be able to lessen the inflammation and necrosis resulted from H2O2 in bleaching gel in Wistar rats' dental pulp tissue [112]. Noteworthy, by preventing cellular oxidative stress and inflammatory pathways that led to pancreatic damage, carvedilol prevented L-arginine-induced acute pancreatitis in a rat model [113]. It has been documented that the gastro-protective action of carvedilol against aspirin-induced stomach injury and indomethacin-induced acute intestinal damage in rats might be ascribed to its anti-inflammatory and antioxidant characteristics, which influenced the NF-kB/COX-2/iNOS pathways [114, 115]. In a rat model of ulcerative colitis, carvedilol ameliorated the colon's architecture and increased the number of mucus-producing goblet cells (GCs). The suppression of oxidative stress, fibrosis, inflammation and barrier dysfunction might be responsible for this anti-colitic action [116].

4.9. On glucose homeostasis

In high fat diet (HFD)-induced obese mouse model, carvedilol ameliorated glucose tolerance and insulin sensitivity through the management of chronic adrenergic overdrive and hyperleptinemic conditions [117]. Moreover, through the suppression of oxidative stress, nuclear factor kappa B (NF-κB), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and proinflammatory cytokines, carvedilol could protect mice from STZ-induced pancreatic β-cell destruction and type I diabetes [118].

4.10. On lungs

In an experimental model of pulmonary thromboembolism in isolated perfused rabbit lungs, carvedilol's vasodilatory actions on pulmonary arterial vessels resulted in enhanced capillary filtration coefficient due to increased precapillary resistance and improved endothelial permeability [119]. In the same context, by regulating P-AKT/mTOR/TGFβ1 signaling and the associated inflammatory and fibrotic consequences, carvedilol mitigated silica-induced lung fibrosis in male Sprague Dawley rats [120]. In human bronchial epithelial cells (BEAS2B), carvedilol might control RhoA/ROCK signaling activity and protect against lipopolysaccharide (LPS)-induced acute lung injury (ALI) [121]. Likewise, carvedilol alleviated the adverse effects in sepsis-induced ALI in rats through high mobility group box 1 (HMGB1)/ soluble receptors for advanced glycation end product (s-RAGE) interaction [122].

4.11. On testes

A study reported that carvedilol could mitigate testicular impairment and disrupted spermatogenesis in rats with adjuvant rheumatoid arthritis via modulating AMPK/ERK and PI3K/AKT/mTOR pathways [123]. As well, carvedilol could ameliorate cyclosporine-, cadmium- and aluminum- induced testicular toxicity in male Wistar rats through modulating the proinflammatory cytokines, Nrf2/HO-1 pathway and apoptosis [124-126].

4.12. On eyes

In a cellular model of diabetic retinopathy, carvedilol has been found to activate the Nrf2/ antioxidant response element (ARE) pathway in retinal pigment epithelial cells and prevent high glucose-induced oxidative stress and apoptosis [127]. Furthermore, in C57BL/6J mice subjected to optic nerve injury (ONI), carvedilol enhanced the survival of retinal ganglion cells through apoptosis signal-regulating kinase-1 (ASK1) and MAPK pathway [128]. Also, it has been documented that carvedilol can be used in glaucoma treatment as it could reduce elevated intraocular pressure [129]. Another study suggested that carvedilol can be used for the management of retinitis pigmentosa (RP) as it ameliorated the deficient visual motor response (VMR) of the RP larvae and increased their rod number [130]. The pharmacological actions of carvedilol are outlined in Table 2.

5. Adverse effects

Compared to other β-blockers, carvedilol is associated with fewer adverse effects that are dosage-related, typically manifest early in the therapeutic regimen, and have a lower incidence. Asthenia, malaise, bradycardia, dyspnea, and malaise (caused by β-blockade) as well as postural hypotension, headache and dizziness (caused by the drug's vasodilatory actions) are the most often reported adverse events [139].

6. Drug-drug interactions

Carvedilol has comparatively few medication interactions. Combination with fluoxetine, a selective serotonin reuptake inhibitor and a potent inhibitor of cytochrome P450 2D6 (CYP2D6), results in a significantly increased bioavailability of carvedilol and subsequently elevates its severe adverse effects [140]. It is well known that carvedilol can inhibit the activity of P-glycoprotein (P-gp), a membrane transporter protein that is essential for the removal of medications and other chemicals from cells, especially those found in the blood-brain barrier, liver, kidneys and intestine resulting in enhanced effects and toxicity of some drugs that are P-gp substrates such as digoxin and cyclosporine [141, 142].

Table 2: Pharmacological actions of Carvedilol

	Target	Action	Effect
Carvedilol	β-adrenergic receptors	antagonist	-Reduce heart rate, contractility, oxygen demand, ROS formation and lipid peroxidation [131] -Ameliorate myocardial remodeling in heart failure [10] -Anti-apoptotic through enhancing Bcl-2 expression [132] - Antifibrotic through suppression of TGFβ1 [65] - Anticancer through prevention of ERK translocation [102]
	α_1-adrenoreceptors	antagonist	-Vasodilatation -Lower blood pressure [10] -Inhibit oxidative stress [133]
	β-arrestin2	biased-agonist	-Improve survival after myocardial infarction [134] -Inhibit cardiac cell apoptosis [135] -Enhance insulin action [29]
	calcium channels	antagonist	-Increase blood flow in cutaneous circulation [136]
	potassium channels	antagonist	-Antiarrhythmic [137] -Promote insulin release [138]

7. Conclusion and future perspectives

The former preclinical findings showed novel actions of carvedilol in ameliorating several disorders and modulating multiple signaling pathways. Advanced techniques like omics technologies and high-throughput screening can uncover novel molecular targets and pathways modulated by carvedilol, enhancing our understanding of its multifaceted effects. Additionally, the research into its role in modulating the immune response and reducing fibrosis may open new avenues for treating chronic inflammatory and fibrotic diseases. Investigating the potential of carvedilol in combination therapies can reveal synergistic effects with other drugs, optimizing treatment regimens for cardiovascular and other systemic diseases. Overall, continued preclinical studies will be pivotal in fully harnessing carvedilol's therapeutic potential and expanding its clinical applications.

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