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Polyphenols as Therapeutic Approach to High Altitude Mediated Skeletal Muscle Impairments

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ABSTRACT

Skeletal muscle impairments at high altitudes resulted into various consequences in un-acclimatised individuals thus hampering their physical activities by imposing severe oxidative stress, skeletal muscle atrophy, mitochondrial dysfunction/autophagy, and regeneration disability. Researchers have described many natural and synthetic supplements to alleviate oxidative stress-induced muscle impairments. In this review article we are focusing on the skeletal muscle impairments and their alleviation by using natural polyphenols. Polyphenols are plant-based compounds showing anti-oxidative and anti-inflammatory properties like Curcumin, Catechins, Resveratrol, Quercetin and Salidrosides appear to mainly act by reversing oxidative stress and mitochondrial dysfunction eventually ameliorate skeletal muscle impairments under various imposed pathological conditions. This review also drew attention on the molecular targets of polyphenols and their possible therapeutic effects in preventing HA induced muscle impairments. Unavailability of suitable intervention, there is a need to find a probable solution having highly protective anti-atrophic, anti-oxidative, anti-inflammatory properties with the tint of performance enhancer.

Keywords: Polyphenols; Skeletal muscle atrophy; High altitude; Oxidative stress; Mitochondria

1. INTRODUCTION

Skeletal muscle is the longest contractile tissue consists of various integrated tissues including myofibers, blood vessels, nerve fibers, and connective tissue which support voluntary movements and locomotion. Millions of people travel to HA every year for amusement, exploration, and troops for guarding at HA boundaries. Extreme environmental conditions prevailing at HA induce skeletal muscle atrophy and others in an un-acclimatised person[1-3]. Studies have also revealed that at extreme environmental conditions, impaired skeletal muscle physiology decelerate physical activity[2].These HA provoked skeletal muscle deterioration includes elevated reactive oxygen species (ROS), muscle mass wasting, mitochondrial dysfunction and regeneration disability[3-4]. Earlier research also envisaged a massive leakage of highly reactive oxidizing agents from mitochondria owing to inadequate supply of final electron acceptor in electron transport chain leading to superfluous oxidative damage of protein, lipid, and DNA[3]. Previous studies have also emphasised that elevated intracellular calcium levels accelerate calpain proteolytic activity under hypobaric hypoxia in rat skeletal muscle[5]. In addition to that, mitochondria's structural and functional proteins became malfunctioning and ultimately deteriorated cellular metabolism and bioenergetics at high altitude[6].This changed mitochondrial membrane potential allowed free transportation for protons without generating ATP under hypoxia[7]. Some authors have also suggested that insufficient oxygen supply yields accelerated Myogenic Differentiation factor (MyoD) degradation and inhibits myogenic differentiation leading towards hampering in skeletal muscle regeneration after damage[8]. High altitude-induced skeletal muscle atrophy, mitochondrial dysfunction, regeneration disability ultimately result in declined physical performance in alpinist.

In the last decade polyphenols, a natural flavonoid, which is abundantly available in edible plants have shown great potential in therapeutics due to their anti-oxidative and anti-inflammatory properties. They are also vital for health as they regulate metabolic disorders, chronic illness, obesity, cancer, cachexia, and sarcopenia etc.[9]. Considerable attention has been paid to investigate the effect of curcumin, catechins, resveratrol, quercetin and salidroside in skeletal muscle impairments however, poorly investigated their efficacy in humans[10]. In brief, the literature about these Polyphenols studies strongly suggests that their supplementation prevents as well as ameliorate muscle damage by reducing oxidative stress and inflammation. Several publications have come in recent past where polyphenols are portrayed as a performance enhancer because of maintaining mitochondrial homeostasis in different pathological conditions[11]. Future research is needed to delineate the regeneration properties of these polyphenols.

Many therapeutic interventions are under investigation to alleviate HA induced muscle damage and to improve ergogenic response. This review highlights the usefulness of these polyphenols as possible therapeutic agents for high altitude-induced muscle damage. To the best of our knowledge, no

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previous review article has explicitly explained polyphenols as therapeutic agents for HA provoked skeletal muscle impairments.

2. HYPOBARIC HYPOXIA INDUCED SKELETAL MUSCLE IMPAIRMENTS

Although, skeletal muscle tissue can adapt under hypoxia by switching itself from aerobic to anaerobic metabolism through gradual ascend and a long stay at HA[9]. Despite that, traveling at high altitude, i.e. above 3000 m - 3500 m, HH the main pathogenic factor elicits acute mountain illness symptoms which include headache, nausea, sleep disturbances and fatigue resultant into physical activity lessening as shown in (Fig. 1)[1-2]. Oxygen is a very essential ingredient for cellular aerobic respiration for the production of energy in the form of ATP.

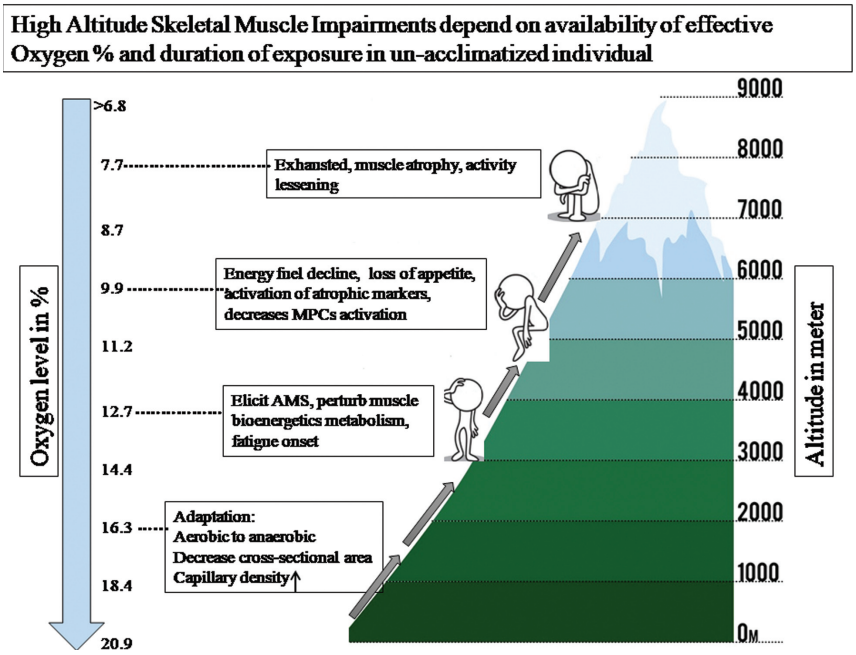

Figure 1. Skeletal muscle adaptation and impairments at high altitude[18].

High altitude provoked oxidative stress is a well-documented fact that perturbs oxidant (ROS)-antioxidant (thiols) balance. Protein oxidative modifications accumulate non-functional proteins and advance oxidative protein products (AOPP) which accelerate the up-regulation of endoplasmic reticulum stress markers such as Heat shock protein (HSP60), HSP70 and 78-kDa glucose-regulated protein (GRP78), further activated proteolysis pathway[12]. Muscle mass loss occurs because of excessive protein degradation and decreased protein synthesis[5]. Several queries still need to be addressed regarding protein synthesis rate at high altitude. A study published by our lab had shown a significant increase in key regulator of protein synthesis, Protein kinase B (Akt), pAkt, p70S6Kinase as well as proteolysis biomarkers, Glycogen synthase kinase (GSK-3β), muscle-specific E3 ligases (Mafbx-1 and MuRF-1) under chronic hypobaric hypoxia in skeletal muscle of rat model. ROS induces increase in the resting cellular calcium concentration which in turn increases calcium dependent non-lysosomal cysteine protease calpain enzyme activity[13]. Inflammatory cytokines TNF-α, Interleukin-6 (IL-6), and Tumor growth factor (TGF-β) promote NF-κB nuclear translocation and activate ubiquitin proteosome pathway (UPS)[11]. To conclude, activation of UPS and calcium dependent calpain proteolytic pathways are accountable for hypobaric hypoxia induced skeletal muscle atrophy.

High altitude exposure decreases mitochondria number to reduce ROS production and tissue damage[14]. Literature findings of high altitude exposure showed an increase in membrane potential, a decrease in stability of mitochondrial membrane and altering electron transport chain (ETC), but remains obscure regarding mitochondrial inner membrane and non-specific mitochondrial permeability[7]. Peroxisome proliferator-activated receptor-gamma coactivator (PGC-1α) a master regulator of mitochondrial function and biogenesis down-regulates at an ascend above 6400m indicating reduced mitochondrial biogenesis and, ETC complex 1,4 and Uncoupling protein 3 (UCP3)[14]. Furthermore, HA induced mitochondrial membrane potential might play an important role to deport cytochrome C from mitochondria to cytoplasm followed by cell apoptosis an interesting area of research.

Satellite cells (SCs) or myofiber precursor cells (MPCs), occur beneath the basal lamina and got activated in response to external stimuli (damage). SCs proliferate as myoblast then migrate to the targeted region of muscle fiber and fabricate into myotube after differentiation and fusion. Satellite cells show a characteristic protein Pax7. The expression level of MyoD, Pax7 and Myogenic factor 5 (Myf5) in satellite cells make a decision to differentiate or remain in proliferative phase or convert into quiescent satellite cells[15]. Satellite cell volume density increases after 8weeks of exposure over 5000m altitude[16]. Whereas reference15 analysed various aspects of muscle regeneration at HA and reported that human skeletal muscle regeneration capacity weakens above 5000m because of decreased satellite cell activation consistent with their decreased myogenicity and fusion ability, yet mechanism unsought[17]. Further experiments need to explain these findings which might be helpful to increase satellite cell activation to alleviate HA muscle atrophy.

3. NATURAL POLYPHENOLS MIGHT PREVENT AS WELL AS ABOLISH SKELETAL MUSCLE IMPAIRMENTS

3.1 Curcumin has Promising Therapeutic Potential for Skeletal Muscle

Curcumin, a natural flavonoid from spice turmeric, has multidirectional therapeutic potential such as anti-oxidant, anti-inflammatory, anti-diabetic, anti-cancer, etc. Curcumin has proven its credentials as a wonderful therapeutic agent that alleviates ROS mediated oxidative damage of lipid; protein and DNA (Fig. 2) and is believed to be associated with diverse chronic pathological complications. The literature on curcumin effects on skeletal muscle shows a variety of approaches with

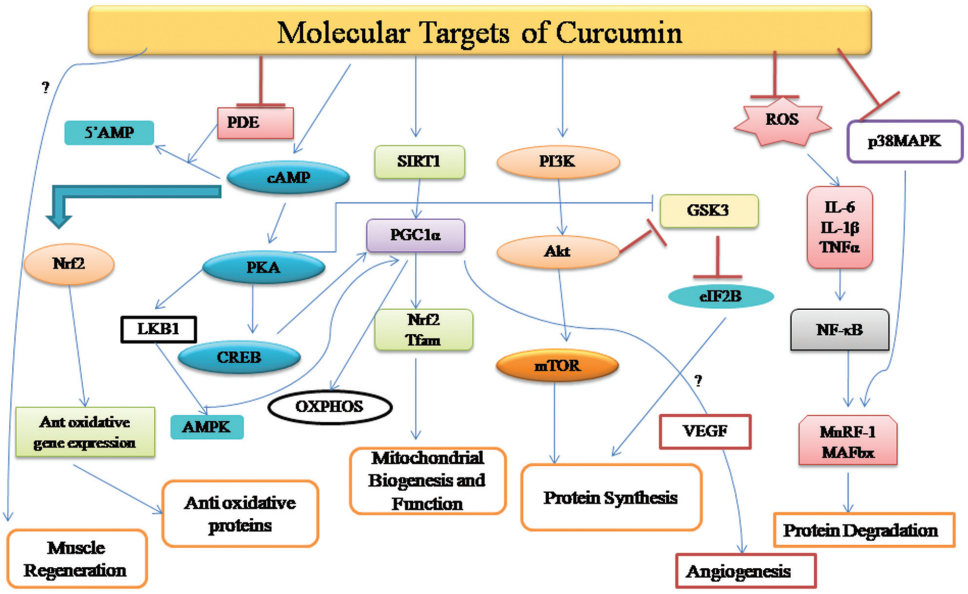

Figure 2. Cellular molecular biomarkers modulated by curcumin supplementation.

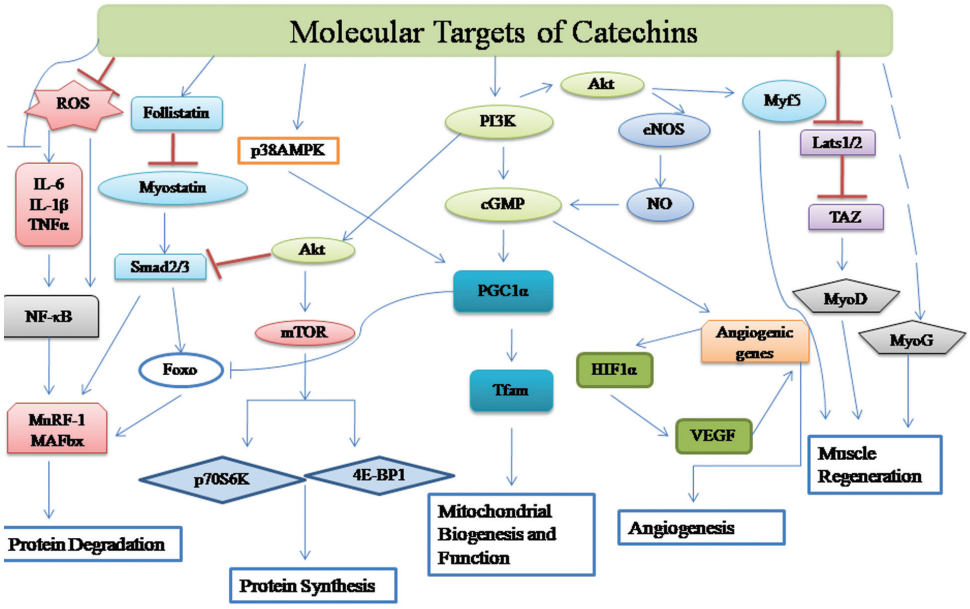

Figure 3. Cellular molecular biomarkers modulated by catechins/epicatechins supplementation.

numerous experimental modalities such as exercise, LPS, TNF-α, chronic obstructive pulmonary disease (COPD), diabetes, high fat-fed diet, downhill running and others. Oral administration of curcumin (dose 3mg/BW) in C57BL/6 mice immediately after downhill running reduces oxidative muscle damage by lowering plasma level of creatine kinase (CK), lactate dehydrogenase (LDH). Curcumin also significantly decreases hydrogen peroxide concentration and down regulates NADPH oxidase mRNA expression[19]. Furthermore, curcumin (100mg/kg BW) attenuates skeletal muscle damage by ischemia/reperfusion injury in Wistar rat by maintaining anti-oxidant reduced glutathione (GSH) level, anti-oxidative superoxide dismutase (SOD) & catalase enzyme consequently reduce lipid and protein oxidation. In addition, plasma level of pro-inflammatory cytokines, TNF-α and IL-1β significantly reduce after curcumin administration[20]. Additionally curcumin alleviates LPS induced muscle wasting by modulating calpain-, cathepsin L-, and proteasome-dependent muscle proteolysis as well as NF-κBp65 mediated proteolysis pathway as a result down-regulation of Atrogin-1 and MuRF-1[21]. Motor-driven rodent treadmill exercise induced muscle damage alleviates by a water soluble curcumin formulation administration for 6weeks accompanied by improved antioxidants level and improve performance as well by maintaining expression level of nuclear factor erythroid 2-related factor 2(Nrf2)[22].

Curcumin supplementation with endurance training activates deacetylation of PGC 1alpha promotedby5′AMP-activatedprotein kinase (AMPK) and SIRT1ultimately modulates the mitochondrial biomarkers cytochrome oxidase (COX) IV, citrate synthase (CS) enzyme activity; OXPHOS (oxidative phosphorylation) subunit expression, and mitochondrial DNA (mtDNA) copy number. Curcumin regulates mitochondrial biogenesis by increasing the level of cyclic adenosine 3′-, 5′-monophosphate (cAMP) and phosphorylation of cAMP response element binding protein (CREB) and liver kinase B-1 (LKB-1)[23]. Oral supplementation of curcumin restores mitochondrial homeostasis by PGC1alpha/SIRT3 up-regulation and prevents skeletal muscle dysfunction in COPD rats[24].

This has been previously assessed only to a very limited extent because contradictory studies are also available regarding curcumin regeneration potential. Additionally, curcumin ameliorates oxidative stress and increases expression of MyoD, myf5 and myogenin lead to proliferation and differentiation under HH but the mechanism of regeneration remains to uncover[25]. Future investigations might be useful to alleviate HA mediated skeletal muscle impairments with curcumin supplementation.

3.2 Catechins Supplementation Revealed Multi-Targeted Therapeutic Potential in Skeletal Muscle

Globally green tea, Camellia sinensis is one of the three major beverages, and catechins are the active ingredient and main secondary metabolites. Catechins components are epicatechin (EC), epigallocatechin (EGC), epicatechin gallate

(ECG), and epigallocatechin gallate (EGCG). Catechins have a unique property to scavenge ROS more efficiently by virtue of high number of phenolic groups (-OH)[26].

In the last decade catechins have attracted much attention from research teams regarding its therapeutic effects in skeletal muscle oxidative stress, mass, strength and performance enhancement (Fig. 3), mainly by: (1) Scavenging ROS produced by aging, cachexia, sarcopenia, and physical exercise, consequently reducing protein, lipid and DNA damage caused by excessive accumulation of highly reactive free radicals; (2) maintaining protein degradation by restoring the activity of ubiquitin E3ligase (MuRF-1/MAFbx), Calcium-dependent chymotrypsin and calpain eventually attenuates skeletal muscle atrophy[27-28] ; (3) Upregulate PGC-α, a potent regulatory transcription factor augmenting mitochondrial function and biogenesis in skeletal muscle and improve aerobic exercise capacity[29];(4) promoting the activation and differentiation of muscle-derived stem cells and accelerating muscle regeneration. ECG augments level of MyHC (myosin heavy chain), MyoD, myogenin[30]. Previous studies proved catechin's unique quality to maintain skeletal muscle homeostasis as well as enhancing performance. This will be provided a good starting point for investigation and further validation of catechin's therapeutic potential at HA mediated muscle impairments.

3.3 Resveratrol Maintains Oxidative Stress and its Associated Pathophysiology

Resveratrol (3,5,4′-trihydroxystilbene), a naturally occurring polyphenolic compound has two *cis* and trans isomer in which *trans*-resveratrol is active from, found in significant amounts in red grapes, berries, peanuts, and other plant sources as well as in red win[31]. Resveratrol maintains skeletal muscle physiology under aging and disease conditions like cancer, heart failure, COPD, Duchenne muscular dystrophy (DMD), chronic kidney disease (CKD) and obese sarcopenia etc[32]. A large number of existing studies in the broader literature has examined in vitro and in vivo studies further confirmed that Resveratrol treatment can prevent ROS and pro-inflammatory cytokine (TNFα, IL-1β, IL-6), provoked E3-ubiquitin ligases mediated protein degradation as shown in (Fig. 4)[32-33]. Besides, resveratrol has shown its anti-atrophic role by inhibiting NF-κB activity and Mafbx/MuRF1 expression. Furthermore, resveratrol increases the expression of SIRT1 which ultimately activates AMPK and regulates muscle wasting and inflammation in COPD rats[34]. Several studies suggest that resveratrol treatment increases the muscle insulin sensitivity by down regulating the level of pro-inflammatory cytokines and up-regulating the protein synthesis in response to the increased level of Akt, AMPK and SIRT1 in cachexia induced atrophy[33]. In addition, resveratrol regulates mitochondrial function and biogenesis via SIRT-1/PGC1alpha signaling pathway in heart failure and increases muscle performance as well[35]. More detailed inspection of the literature on resveratrol muscle regenerative capacities, however, reveals a number of gaps and shortcomings. Bennet et al., reported modest but potentially important benefits of resveratrol supplementation in improving skeletal muscle regeneration but there is still considerable controversy surrounding in resveratrol mediated satellite cell proliferation and differentiation in skeletal muscle[36].

3.4 Quercetin Maintains Physiological Anti-Oxidant And Mitochondrial Homeostasis

Quercetin is a natural flavenoid possess anti-oxidant and anti-inflammatory properties because of its free radical scavenging and hydrogen donating properties. Oral supplementation of quercetin protects skeletal muscle from ischemia/reperfusions injury by maintaining the physiological concentration of anti-oxidative enzymes[37]. Furthermore, quercetin supplementation improves anti-inflammatory response and anti-oxidant enzymes in murine C2C12myoblast and C57BL/6 male mice by up-regulating heam oxygenase-1 (HO-1) and Nrf2 respectively. Quercetin abrogates the activation of HO-1 in Nrf2 deficient mice[38]. In addition, long term quercetin dietary enrichment could able to reverse only 50 per cent of dystrophin related skeletal muscle losses in X-linked muscular dystrophy mice[39]. Despite that quercetin supplementation inhibits muscle inflammatory cytokine TNF-α and monocyte chemoattractant protein 1(MCP-1) release following down-regulated expression of Atrogin-1/MuRF1 and prevents the obesity-induced reduction of skeletal muscle mass in high fat-fed diet C57BL/6 male mice[40]. Correspondingly quercetin supplementation increases cell

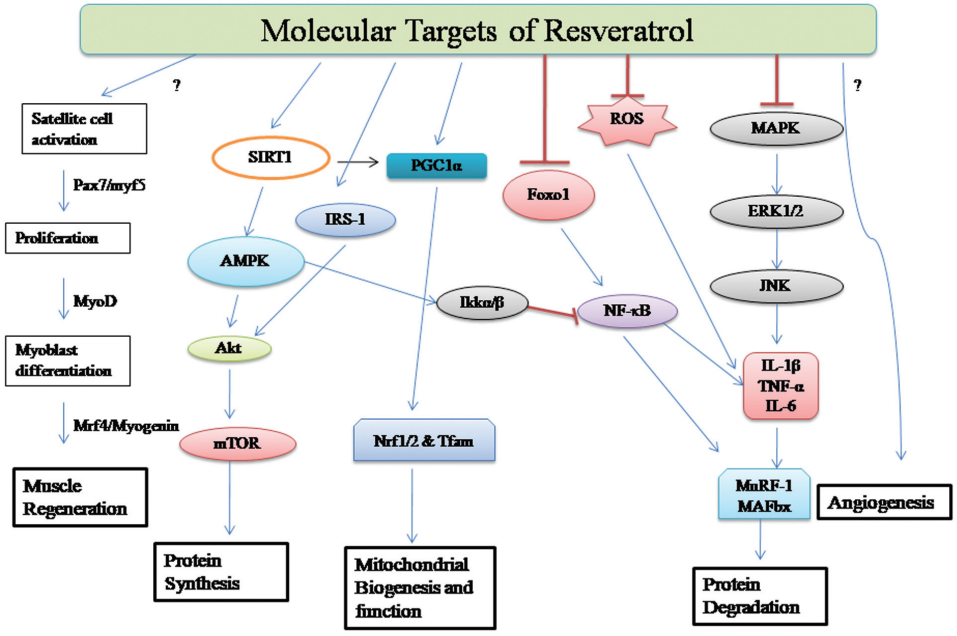

Figure 4. Cellular molecular biomarkers modulated by resveratrol supplementation.

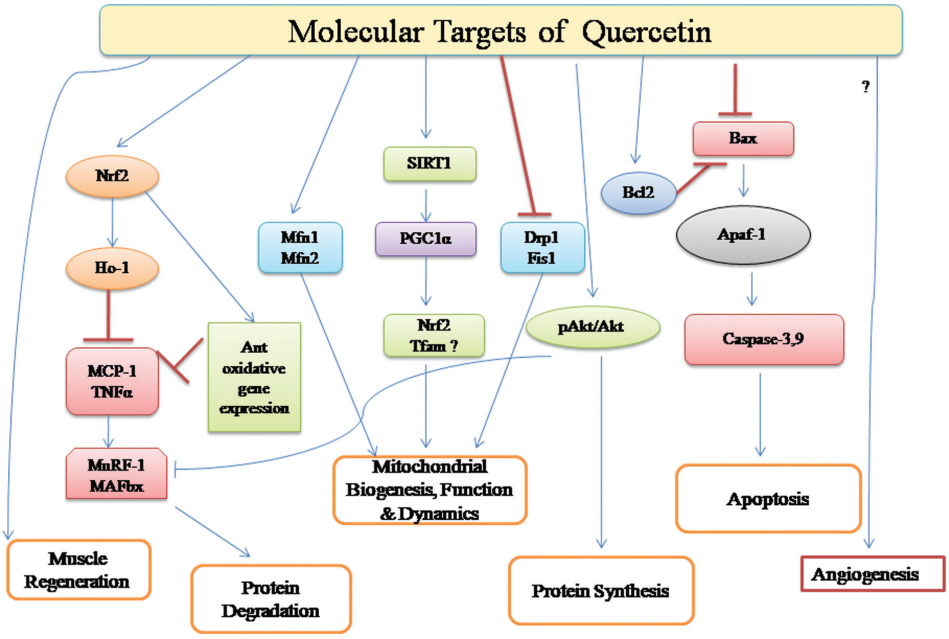

Figure 5. Cellular molecular biomarkers modulated by Quercetin supplementation.

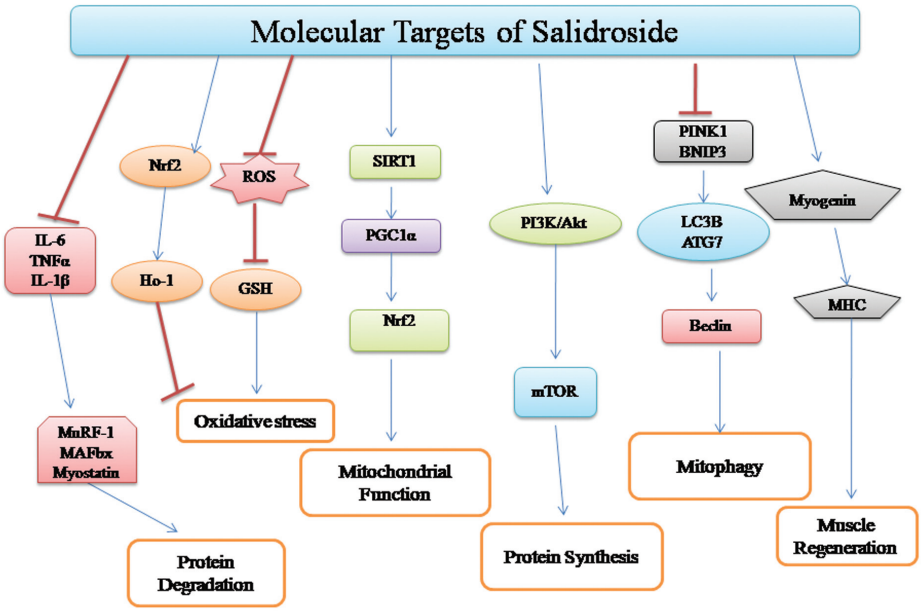

Figure 6. Cellular molecular biomarkers modulated by Salidroside supplementation.

viability and exerts anti-apoptotic effects on dexamethasone-treated C2C12 cells by regulating Bcl2, Bax, Apaf-1, caspase-3,9 and mitochondrial membrane potential ($\Delta\Psi m$) result in attenuation in cellular oxidative stress and skeletal muscle atrophy[41]. Quercetin prevents disuse muscle atrophy in denervated mice by improving anti-oxidative capacity and decreasing hydrogen peroxide production ultimately restore protein synthesis marker pAkt/Akt and down-regulates degradation marker MuRF-1as shown in (Fig. 5)[42].

Literature has many controversies regarding quercetin's mitochondrial effects. This has also been explored in prior studies about quercetin effects on mitochondrial function, that chronic low dose of quercetin up regulates PGC-1α expression followed by improving bioenergetics and skeletal muscle mitochondrial function[43]. In addition up-regulated PGC1α and SIRT1 by oral quercetin supplementation also increases mitochondrial biogenesis in brain and muscle result in improvement in muscular performance[44].In contrast, quercetin restores disuse muscle atrophy mediated PGC-1α activity but no effects on mitochondrial transcription factor A (TFAM) and other mitochondrial biogenesis markers in denervated mice[42]. Probably because quercetin failed to stimulate mitochondrial biogenesis in human skeletal muscle and mouse primary cortical neorons[45]. Despite this, high dose of quercetin can enhance mitochondrial biogenesis by restoring PGC-1α pathway, mitochondrial dynamics by restoring fusion (mitofusin 1 & mitofusin 2)/ fission (Dynamin-related protein 1, Mitochondrial fission 1 protein), also maintains ETC complex protein and ATP level under HH (5000 m 7day) in SD rats hippocampus[46]. Whereas a study reported that oral supplementation of quercetin (25 mg/kg BW) abrogates exercise-induced skeletal muscle adaptation in Wistar rat by lowering the SIRT1 level in rat model[47]. Some studies reported positive effects and others no effects of quercetin supplementation that's why there is need to explore the quercetin mitochondrial effects and skeletal muscle performance as well. As far as we know, no previous research has investigated quercetin mediated muscle precursor cell activation. A number of questions, regarding quercetin effects on skeletal muscle regeneration, remain to investigate.

3.5 Solidroside Prevents Oxidative Stress Induced Muscle Atrophy and Maintains Muscle Function

Salidroside is another natural plant compound found in *Rhodiola rosea* with superior anti-oxidative and anti-inflammatory properties. Salidroside down regulates muscle atrophic markers MuRF1 and MAFbx along with mitochondrial autophagy genes such as PINK1, BNIP3, LC3B, ATG7, and Beclin1 against denervation induced muscle damage in animal model. In addition salidroside supplementation reduces expression level of pro-inflammatory cytokines including IL-6, IL-1beta and TNF-alpha[48-49]. Interestingly, salidroside increases expression of muscle contractile protein myosin heavy chain (MHC) and myogenesis marker myogenin with increased level of protein synthesis marker mTOR in denervation and COPD

induced muscle atrophy and cancer cachexia[50-51]. Additionally, it also ameliorates insulin resistance by modulating AMPK/PI3K/Akt/GSK3beta pathway in high fat diet induced obesity model and mitigates muscle dysfunction[52]. Despite these therapeutic potential, still salidroside has not been investigated in the high altitude induced muscle atrophy (Fig. 6).

4. CONCLUSION

Hypobaric hypoxia induced skeletal muscle responses show a dynamic feature that is dependent on duration of hypoxic exposure and availability of oxygen percentage. Skeletal muscles are tolerant to hypoxia to a certain limit i.e. 2000 m - 3000 m. Climbing over 3500 m engenders severe oxidative muscle damage and declined in physical performance that demands a promising therapeutic agent. The available literature recommends that bio-active polyphenols with their potential anti-oxidative and anti-inflammatory properties could be a probable solution for high altitude induced skeletal muscle impairments and thereby improving performance.

5. FUTURE PERSPECTIVE

Polyphenols covering many important properties like reducing free radical generation and their associated bio-molecular damages, maintains mitochondrial homeostasis, reduces protein degradation and increases protein synthesis, activates muscle satellite cells which results muscle regeneration. Many polyphenols like Curcumin, Catechins, Resveratrol, Quercetin and Salidroside are natural bioactive compounds having anti-oxidative and anti-inflammatory properties might be effective in HH induced skeletal muscle impairments as depicted in (Fig. 7). This review gives insight into these properties which can further be explored by designing detailed experiments with animal models and later can be translated to humans for alleviating HA induced skeletal muscle impairments.

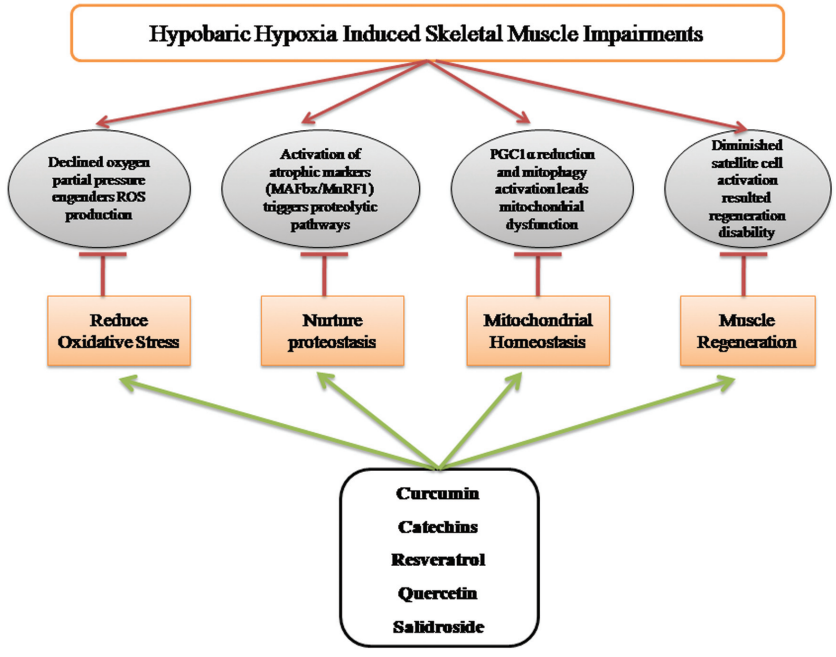

Figure 7. Projected summaries associated between HH induced muscle impairments and possible therapeutic targets of polyphenols.

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