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SELECTIVE ANDROGEN RECEPTOR MODULATOR'S (SARMS) IN THE THERAPY OF CANCER & AGE RELATED MUSCLE ATROPHY

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Abstract: A number of studies have been taken into consideration in the past decades regarding the issue of muscle atrophy due to age related syndrome that is termed as "Sarcopenia" or due to cancer which is termed as "Cancer Cachexia". Several studies have showcased the effectiveness of anabolic steroids in terms of building strength and muscle mass when taken in supraphysiologic doses. Anabolic steroid therapy such as "Testosterone" improves lean body mass and physical performance but the use of anabolic steroids for muscle mass gain also comes with severe adverse effects on health such as potential cardiovascular risks and chances of occurrence of prostate cancer which clearly shows that anabolic therapy is not suitable for long term treatment. The review aims to discuss the advantages of non-steroidal SARMS over the conventional anabolic steroids in the pharmacotherapy of cancer cachexia and sarcopenia.

Index Terms **–SARM'S, Cancer Cachexia, Sarcopenia, Muscle Atrophy.**

I. INTRODUCTION

Androgen receptors are steroid hormone receptors that have significance in tissue diversity.(***Narayanan et al., 2018***) One of the examples of Androgen Receptor ligands includes Testosterone which directly binds to the androgen receptor and activates it causing its effects. Over expression of androgen receptor & metabolism limits the usage of steroidal androgens.(***Narayanan et al., 2018***) Steroidal SARM'S(Selective Androgen Receptor Modulators) are being used since 1940's.(***Bhasin and Jasuja, 2009***) A number of studies showed the abuse of steroidal SARM'S in athletes due to its ability to increase muscle strength & athletic performance but it comes with numerous side effects.(***Pany et al., 2019***) Steroidal SARM'S that promote anabolic activity are widely used to treat cachetic syndrome in various patients. Due to the side effects of these Anabolic steroids on cardiovascular system, prostate, clitoris and hepatic system, they should be replaced with safe alternatives with equal potency.(Wright et al., 2018); ***Thum and Springer, 2011***; ***Blanqué et al., 2014***; ***Evans et al., 2007***) There are a variety of Non-steroidal SARM'S that behave as full agonist to promote bone and muscle diversity, as partial agonist to aid in the maturation of prostate , thereby reducing the chances of prostate cancer. These Non-steroidal SARM's does not bind to cytochrome P19 & 5a-Reductase which helps in non-conversion of testosterone into dihydrotestosterone due to the metabolism.(***Randall, 1994***).(***Bhasin and Jasuja, 2009***) .Various pre-clinical studies have shown the significance of Non-Steroidal SARMS in increasing the muscle mass & bone mass with the ability to spare prostate that shows their efficacy in treating cachexia as well as osteoporosis.(***Narayanan et al., 2018***; ***Yanase, 2016***) In phase-1 clinical trials, modest gains in fat free lean muscle mass have been reported.(***Bhasin and Jasuja, 2009***) In the last two decades, various research and discoveries have been carried out demonstrating the potential of SARMS with greatly reduced unwanted side effects which were observed in the scenario of steroids.(***Narayanan et al., 2018***) SARMs drug therapies are proven to be useful in various diseases such as "Muscle Wasting", "Breast Cancer", "Osteoporosis", "Functional limitations associated with aging", "Chronic diseases". SARMS shows opposite effects on different organ systems. While it produces anabolic effects on muscles and the central nervous system (CNS), it has neutral or antagonistic effects on the

sex tissues like prostate. (***Bhasin and Jasuja, 2009***; ***Narayanan et al., 2018***; ***Aikawa et al., 2015***) Hiking of glucocorticoid levels could trigger the situation of muscle atrophy that have various pathological factors including cachexia. Glucocorticoid related muscle atrophy leads to increase in protein breakdown & decrease in protein synthesis that further leads to the breakdown of fast twitch muscles leading to fall in cross sectional area and myofibrillar protein content in the muscle.(***Schakman et al., 2013***)

1.1 Cancer Cachexia

Cancer Cachexia is described as a metabolic condition that indicates the reduction in skeletal muscle mass that may or may not be accompanied with decrease in fat mass, which consequently brings about decrease in strength & functional status increasing morbidity & mortality in the affected patients.(***Thum and Springer, 2011***; ***Mantovani and Madeddu, 2010***) This phenomenon includes muscle loss, decreased calorie intake, fatigue, anaemia, diversified immune system. Approximately 30-70% of patients present the symptoms of cachexia in the terminal stages of cancer thereafter leading to increased susceptibility to treatment-related adverse effects and poor response to chemotherapy. Since cancer cachexia deteriorates the quality of life(QoL) and survival rate in cancer patients, it is responsible for about 20% of cancer demise.(***Barajas Galindo et al., 2017***; ***Park et al., 2019***) Cancer induces wasting in muscle that resurfaces in the early stage of the disease resulting in the decadence of physical function along with other harmful clinical consequences.(***Dobs et al., 2013***) Dietary supplementation & increasing calorie intake are alone not enough for the treatment of cancer cachexia.***(Dodson et al., 2011)*** Several drugs failed in showing promising results in clinical trials that include eicosapentaenoic acid, bortezomib and anti- tumor necrosis factor (TNF)-α monoclonal antibody, cyproheptadine, hydrazine, metoclopramide, and pentoxifylline.(***Mantovani and Madeddu, 2010***; ***Madeddu and Mantovani, 2009***)

A variety of promising agents are under clinical trials such as: ghrelin analogs, selective androgen receptor modulators(e.g. Ostarine), as well as anti-inflammatory drugs such as thalidomide, OHR, anti-interleukin antibody(e.g. Anti IL-6 antibody), cannabinoids, and omega-3 supplements, β-blockers such as Espindolol and antimyostatin peptides. The significant positive consequences were stimulation of appetite, weight gain, increase in mass of muscle and function, modulation of inflammation, and quality of life.(***Mantovani and Madeddu, 2010***; ***Madeddu and Mantovani, 2009***; ***Molfino et al., 2019***; ***Argilés et al., 2017***; ***Stewart Coats et al., 2016***) A major proportion of these agents do not directly interfere with the muscle loss.(***Crawford et al., 2016***) Circulating macrophage inhibitory cytokine 1/growth differentiation factor 15 & ZRT/IRT-like protein 14 have proven to be a novel molecular approach in pre-clinical trials but are yet to be tested in humans. The existing data shows that single therapy is not beneficial for treating Cancer Cachexia and hence multimodal approach should be employed.(***Miller and Skipworth, 2019***) Biomarkers of protein synthesis exhibited its efficacy in pre-determining the muscle loss in patients.(***Shankaran et al., 2016***) Nowadays, various techniques such as Dual energy X-ray imaging (DEXA), magnetic resonance imaging (MRI) & computed tomography (CT) have been used to determine the lean body muscle mass with high rate of accuracy.(***Thomas et al., 2020***)

II. PATHOPHYSIOLOGY

At present, the principal theories for the cause of cachetic syndrome are Anorexia and metabolic alterations.(***Dodson et al., 2011***; ***Argilés et al., 2017b***) Figure 1 demonstrates the pathophysiology of Cancer Cachexia. Anorexia leads to the decrease in food intake and with that, other metabolic alterations leads to increase in lipolysis and proteolysis which further leads to decrease in lean body mass and fat mass. This condition directly leads to the weight loss and cachexia.(***M. et al., 2006***)

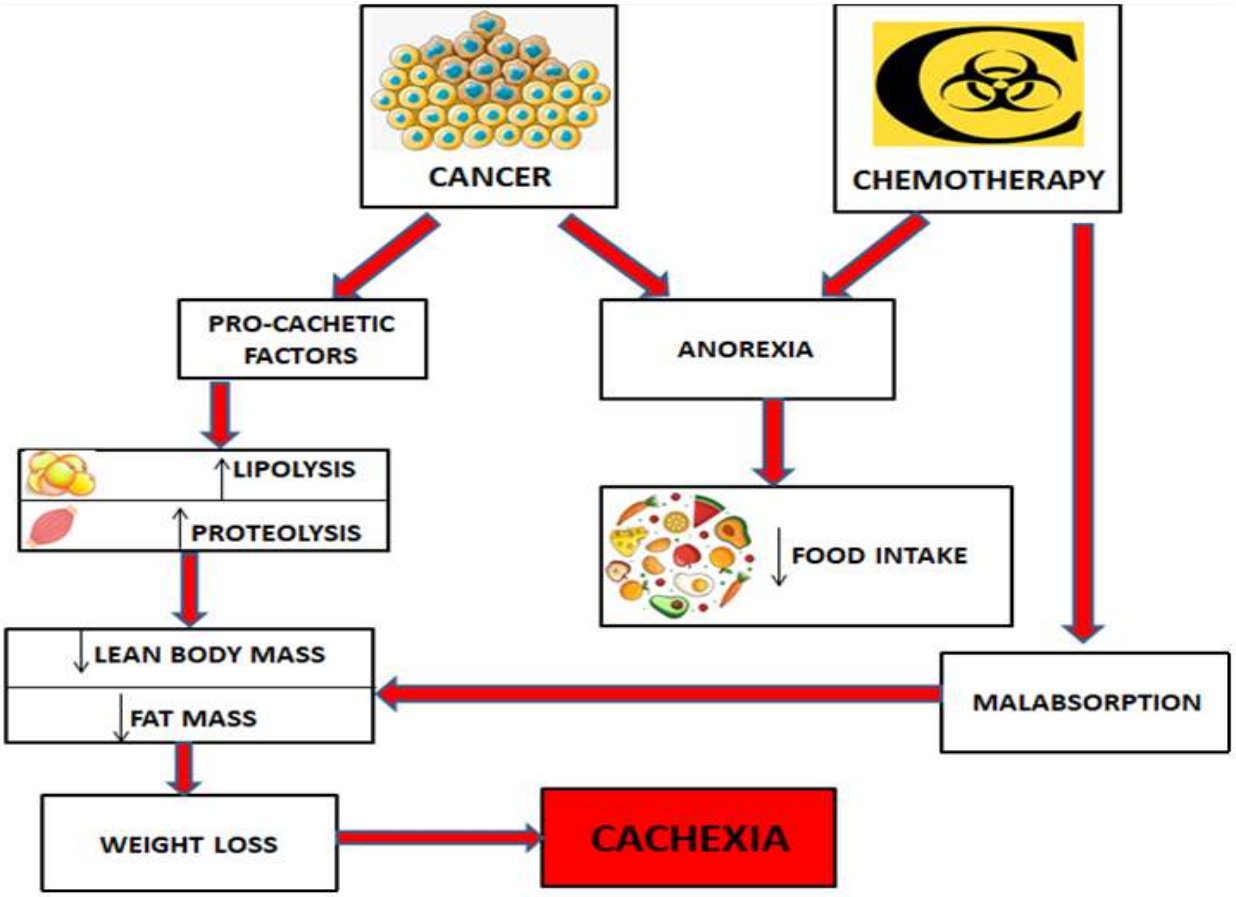
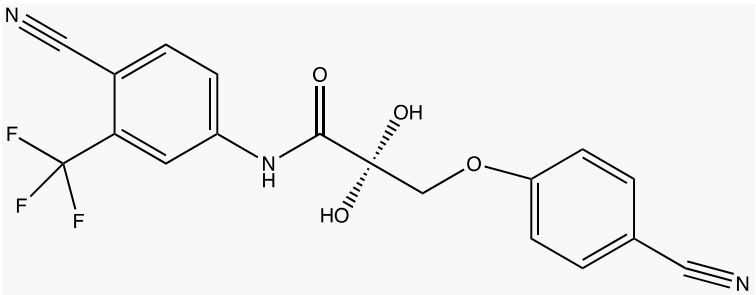


Figure 1. Flow diagram of Cancer Cachexia Pathophysiology

III. PHARMACOLOGICAL INTERVENTION

SARM'S can prove to be an efficacious restorative approach for cancer cachexia & sarcopenia treatment as androgens promote growth in skeletal Muscle mass, but their clinical use is impeded by an absence of tissue specificity and various adverse effects.(***Dubois et al., 2015***; ***Crawford et al., 2016***) Sarcopenia is defined as skeletal muscle disorder in which enhanced loss of lean muscle mass is observed.(***Cruz et al., 2019***) Selective androgen receptor modulators evoke muscle-anabolic effects while showing antagonizing effects on reproductive tissues. SARMS are also available in the form of transdermal patches thus making the administration easy and avoiding the first pass effect of metabolism which is observed in the case of oral administration.(***Dubois et al., 2015***; ***Saeed et al., 2016***) We discuss about the numerous SARM'S compounds that are under pre-clinical and clinical trials.

4.1 GTx-024 (Enobosarm)

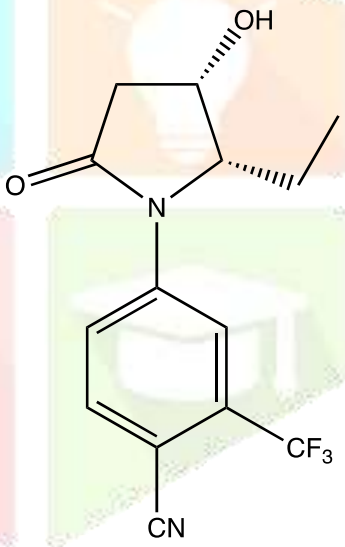


GTx-024(Enobosarm) ***(Wishart DS et al., 2018)***

GTx-024 , a selective androgen receptor modulator which is a non-steroid spares the unwanted effects such as prostate in men and abnormal hair growth in women. GTx-024 is also known around as Enobosarm, Ostarine & MK-2866. It demonstrates tissue specific anabolic effects in muscle and bone formation while decreasing the total tissue fat percentage.(***Zilbermint and Dobs, 2009***; ***Dalton et al., 2011***; ***von Haehling and Anker, 2014***) It has been tested in phase I,II & III trials with favorable results.(***R. and A., 2014***) In a placebo controlled phase 2 clinical trial, Enobosarm showed significant increase in fat free body mass which was showcased by dual energy x ray

absorptiometry and other factors such as physical function, body weight, insulin resistance & safety were also determined.***(Dobs et al., 2013***; ***Dalton et al., 2011***) Dose dependent increase in fat free body mass and physical performance were observed. ***(Dalton et al., 2011)*** Enobosarm exhibit positive effects in bone healing in ovariectomized rats & its short term administration to the osteoporotic patients led to the enhancement of a number of microstructural bone indices, thus showing its potential to be used in osteoporosis therapy.(***Komrakova et al., 2020***; ***Hoffmann et al., 2019***) Similarly, Enobosarm was also tested in POWER-1 & POWER-2 clinical trials. The POWER trials are two similarly curated randomized, double-blind, placebo-controlled, multicenter, and multinational phase 3 trials to evaluate the efficacy of Enobosarm in patients portraying muscle wasting in first-line chemotherapy for non-small-cell lung cancer (NSCLC).(***Crawford et al., 2016***) From these trials, the ability and power of subjects to climb stair improved at day 84 by >=10% from their baseline value.**("Phase III Study of the Effect of GTx-024 on Muscle Wasting in Patients With Non-Small Cell Lung Cancer (NSCLC) - Full Text View - ClinicalTrials.gov," n.d.)** In a study, Enobosarm decreased the release of leptin & adiponectin mRNAs by downregulating their expressions further demonstrating its effect on lipid metabolism intensity. More of the fat free, lean muscle mass can be attained with Enobosarm.(***Leciejewska et al., 2019***) Cancer Cachexia often leads to decrease in calorie intake which leads to the fall in nutritions required in treating muscle wasting. Enobosarm proved to be advantageous when combined with Anamorelin, which is a selective agonist of Ghrelin(Hunger Hormone) leading to increase in body weight as well as muscle mass.(***Molfino et al., 2014***; ***Currow et al., 2018***; ***Advani et al., 2018***)**("The Role of Ghrelin in Cancer Cachexia - Full Text View - ClinicalTrials.gov," n.d.)** In a 26 colon cancer cachexia mouse model, Enobosarm & Histone Deacetylase Inhibitors reduced the cachetic activity and this combination was found to increase lean body mass as well as increase strength.(***Liva et al., 2020***)

4.2 SARM 2f

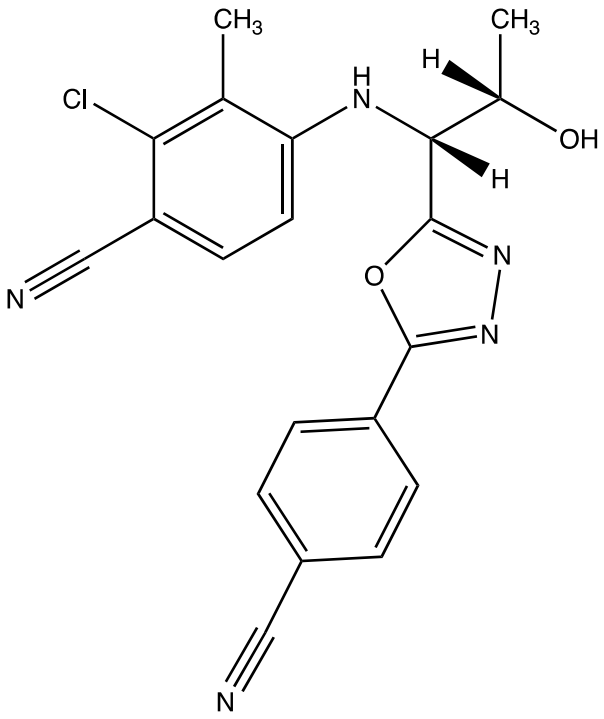


SARM-2f (***Morimoto et al., 2017a***)

SARM 2f is an androgen receptor modulator which is selective and shows anabolic effects and less antagonizing effects on prostate which is under pre-clinical trial. SARM 2f increases lean muscle mass and enhances locomotor activity in rats.(***Morimoto et al., 2020***) In cancer cachexia animal models, SARM-2f showed significant anabolic effect by enhancement of overall body weight in general and skeletal muscle weight in specific. It also did not affect the weight of the seminal vesicles or prostates in the male rats who had undergone castration.***(Morimoto et al., 2017a***) SARM 2f & Testosterone Propionate medication in C26 & G361 cancer cachexia animal models resulted in the increase of body weight, carcass weight, levator ani muscle and lean body mass. ***(Morimoto et al., 2017a***) This showcase the ability of SARM 2f to be used in multimodal approach in the treatment of Cancer Cachexia. In a recent study, oral administration of SARM 2f in cynologous monkey with a dose of 10 mg/kg for 4 weeks proved to increase the body weight by 5% & it also increased lean body mass by 8%. SARM 2f also decreased the plasma lipid levels whereas Testosterone Enanthate dosage demonstrated an increase in low density lipoprotein cholesterol levels.(***Morimoto et al., 2020***) In another recent study that employed rat Hershberger assays & cancer cachexia animal models, SARM 2f treatment exhibited greater activity in contrast to Androgen Receptor in Skeletal Muscle Cells than in Prostate Epithelial Cells. It also restored the sexual behavior in castrated rats & enhanced locomotor activities as well as running

distance.(***Morimoto et al., 2017b***) –SARM 2f leads to improvement of physical performance as well as lean body mass that clearly suggests it's importance in the cancer cachexia & sarcopenia therapy in the future.

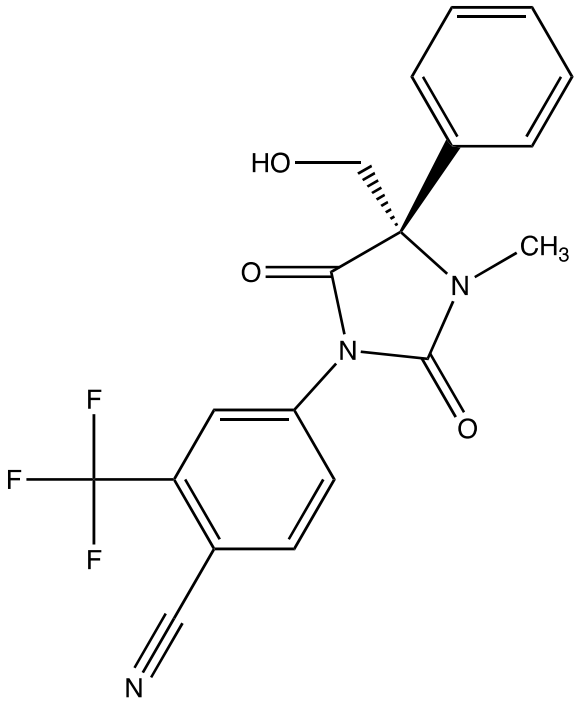
4.3 RAD-140(Testolone)



RAD-140(Testolone) ***(Wishart DS et al., 2018)***

RAD-140 is a selective androgen receptor modulator which is also commonly known as "Testolone". It is a potency selective SARM that provides the benefit of sparing the side effects on sex tissues such as clitoris in females and prostate & seminal vesicles in males. RAD-140 is found to be increasing lean muscle mass & improving physical performance in various pre-clinical models such as rats & monkeys.(***Miller et al., 2011***) It also selectively triggers bone growth & has specificity for muscles over prostate.(***Miller et al., 2011***) Being a potent anabolic agent, it has shown outstanding results in pre-clinical animal models. RAD-140 has demonstrated its benefits in the treatment of breast cancer when given along with "Palbociclib" which is an anti-cancer agent.(***Yu et al., 2017***) SARMS have proven to be an efficacious line of therapy in the treatment of cancer and further more research is being carried out.(***Narayanan et al., 2014***; ***Ponnusamy et al., 2019***; ***Narayanan et al., 2018***) In preclinical studies, RAD-140 also proved to be efficacious in the treatment of neurodegenerative diseases such as Alzheimers.(***K. et al., 2013***; ***Jayaraman et al., 2014***) These studies prove the advantages of SARMS such as RAD-140 to treat cancer proliferation as well as cachexia caused by it. RAD-140 is undergoing phase 1 clinical trials and according to the literature it is expected that SARM therapy will be advantageous over anabolic steroids in the treatment of cancer cachexia.

4.4 GLPG0492



GLPG0492*(Wishart DS et al., 2018)*

In a preclinical study on a mouse model, a selective androgen receptor modulator "GLPG0492" was tested for its effects in treating musculo skeletal diseases such as cachexia & sarcopenia. On the other hand the mice were administered with α-methylprednisolone & Nandrolone to measure their effects. GLPG0492 proved to be as efficacious as with α-methylprednisolone & Nandrolone in improving the strength and the muscle mass of the animal. The results were dose dependent in both the Cases.(***Cozzoli et al., 2013***) In another preclinical study, GLPG0492 was tested for its outcome in the prevention of muscle loss as compared to Testosterone Propionate. GLPG0492 was as effective as Testosterone Propionate.(***Blanqué et al., 2014***) GLPG0492 can be proved to be an effective therapy in the treatment of muscle loss and hence more study and knowledge is required to determine its efficacy in the treatment of musculo skeletal diseases in the future.

4.5 MK-0773 & MK-3984

MK-0773 is a SARM that has proved to be effective in the treatment of age related muscle atrophy (Sarcopenia) by improving lean body muscle mass in females.(***Papanicolaou et al., 2013***; ***Schmidt et al., 2010***) Whereas another SARM "MK-3984" also demonstrated its effects in improving lean body mass.(***Dalton et al., 2013***) More research is required to determine their efficacy and potency. Intervention of proper diet that includes all necessary components & exercise routine which includes workouts and cardio in the SARM therapy of muscle loss has been proven to be advantageous and shows great effects on lean body mass and strength.*(**Argilés et al., 2017b***; ***Yoshimura et al., 2017***)

IV. CONCLUSION

From past decades we have observed the significance and potential of Anabolic Steroids in the production of muscles and athletic performance but due to their side effects they have detrimental effects on health. Long term therapies of Anabolic steroids are not preferred so as to avoid the hazardous effects on various systems. SARM'S have proven to be the safest alternatives for the therapy of cachexia and sarcopenia with least amount of damage caused to the health. SARM'S can be used to treat cachexia without worrying about the negative effects that is faced in the Anabolic steroid therapy. According to the studies conducted on SARM'S, they have proven to be useful in treating the condition of muscle atrophy as well has their implication in treating osteoporosis. The potency of SARM'S in anabolism is almost similar to that of Anabolic Steroids which makes them useful in the therapy of Cancer Cachexia and Sarcopenia. Major research had been conducted on its positive effects and in the upcoming future; SARM'S will demonstrate promising and convincing results and benefits over the usage of Anabolic Steroids.

V. ACKNOWLEDGEMENT

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