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Review Article

Advances in *In-Silico* Analysis of Bioactive Compounds: Metabolic Interactions with genes involved in Prostate Cancer.

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Abstract

As a mutation and genetics-dependent disease Prostate Cancer (PCa) ranks second among all male malignancies while remaining a dominant cause of male cancer fatalities. The BRCA1 and BRCA2 genes work to repair DNA but mutations in these genes make patients more vulnerable to tough types of PCa. BRCA2 mutations increase PCa risk four times more than other mutations including BRCA1 mutations. The tumors with these mutations display good responses to DNA-damaging drugs especially PARP inhibitors that exploit dysfunctional DNA repair mechanisms. Medical research teams connecting traditional herbal meds and modern science have demonstrated cancer fighting potential in many developing nations. Men should prioritize genetic screening due to its role in producing prostate cancer most commonly through abnormalities of important genes such as BRCA1 and BRCA2. A modified state of DNA repair genes leaves the body susceptible to the development of aggressive types of prostate cancer. Research shows that males carrying BRCA2 mutations will develop prostate cancer. DNA-damaging treatments such as PARP inhibitors will enhance the sensitivity of cancers which carry BRCA mutations. Targeting the dysfunctional DNA repair systems of cancer cells enables these medications to direct therapeutic action more precisely which results in improved patient results. Traditional herbal cancer treatment options show growing potential for medical use. Subsequent research will aim to clarify these organic substances' operational mechanisms which will develop new treatment methods combining modern medical science with existing medical knowledge.

Keywords : *Prostate Cancer (PCa), BRCA, DNA Damage Response, Herbal Medicine, Phytochemicals, Anticancer.*

INTRODUCTION

With about 217,730 new cases and 32,050 deaths recorded in 2010, prostate cancer is the most common non-dermatologic cancer and the second leading cause of cancer mortality among men in the United States. Particularly in families with a history of early-onset illness, when first-degree relatives run a 2–2.5-fold greater risk of acquiring the disease, genetic elements play a major role in its risk. Son of dads who live longer than 59 months following diagnosis, had a 38% reduced chance of prostate cancer [1].

Although most occurrences are sporadic, genome-wide research pointing to many risk-associated loci—including 8q24 and 17q—support linkages to ovarian and breast tumors [2]. Furthermore, two to three percent of cases of prostate cancer are caused by mutations in the BRCA1 and BRCA2 genes; carriers have much higher risks. The Breast Cancer Linkage Consortium initially exposed the relationship between BRCA mutations and prostate cancer by pointing up higher incidence rates in families with a history of ovarian and breast tumors. Found on chromosome 13q12, the gene BRCA2 was discovered in 1995 and codes for a protein essential for DNA repair via homologous recombination [3]. For DNA damage repair, it helps RAD51 to be localized and activated; BRCA2-deficient cells find it difficult to get RAD51 to the nucleus, therefore compromising DNA repair.

ROLE OF BRCA GENES IN PROSTATE CANCER METASTASIS

Aggressive types of prostate cancer, especially in BRCA mutation carriers who show a greater prevalence of high-Gleason-score tumors and a quicker progression to castration-resistant prostate cancer (CRPC), are associated to this dysfunction. Research indicates that BRCA2 mutations

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greatly raise prostate cancer risk; carriers have a relative risk of 4.65. By functioning as an androgen receptor co-regulator and thereby reducing insulin-like growth factor receptor expression, BRCA1 further contributes to prostate cancer by further impacting cancer proliferation [4]. BRCA mutations have therapeutic ramifications as malignancies with these mutations react better to DNA-damaging therapies, particularly PARP inhibitors, which take use of the compromised DNA repair systems in these tumors. Tailored treatment plans and genetic counselling for at-risk families depend on an awareness of the functions of BRCA genes in prostate cancer [5].

Focusing on epithelial ovarian cancer (EOC) and prostate cancer, "BRCA Mutations in Ovarian and Prostate Cancer: Bench to Bedside" stresses the vital part DNA damage and repair systems play in cancer. With mutations in BRCA1 and BRCA2 frequent, EOC—especially the high-grade serous subtype—often shows flaws in DNA damage response (DDR) pathways. These alterations fundamentally affect treatment strategies and genetic cancer risk [6]. Standard therapy for EOC and also useful for metastatic castration-resistant prostate cancer with DDR changes are PARP inhibitors. Along with continuous study on the wider consequences of DNA repair pathways, the review underlines the increasing relevance of genetic testing in guiding therapeutic decisions and the requirement of accurate biomarkers to predict treatment responses [7].

In contrasting homologous recombination (HR) and nonhomologous end joining (NHEJ) throughout several cell cycle stages, the dynamics of DNA repair methods are discussed. While NHEJ, which may occur all through the cell cycle, is more error-prone and usually operates in the G1 phase, HR is exact and depends on sister chromatids accessible in the S and G2 phases. Newer elements like PAXX and MRI/CYREN are among the more diverse variety of proteins involved in NHEJ, according recent studies, than formerly thought. The degree of DNA end resection, affected by different proteins either enhancing or blocking the pathways, determines whether HR or NHEJ should be used for double-stranded break repairs [8]. Especially in relation to BRCA mutations, where the simultaneous inactivation of certain gene pairs might result in cell death, the paper addresses the idea of synthetic lethality—a notion taken advantage of in treatments such as PARP inhibitors. This approach emphasizes the possibility of focusing on extra genes in the HR pathway to improve the efficacy of therapy for tumors marked by BRCA mutations [9].

Emphasizing the idea of synthetic lethality, the book addresses Rad52's potential as a tumor-specific therapeutic target in BRCA2-deficient malignancies. Rad52's function in mending base mismatches and insertion-deletion loops across the mismatch repair (MMR) pathway means that inactivation of Rad52 in these cells might cause major problems with cellular proliferation. By inhibiting Rad52, DNA mistakes might be greatly lowered and mutation fixation avoided [10]. Rad52's participation in several DNA damage response (DDR) channels begs for problems regarding its exact function in HR-independent systems. With mitoxantrone emerging as a possible Rad52 inhibitor, recent research simply that stopping the interaction between RPA and Rad52 may compromise DNA repair mechanisms. Moreover, other genetic connections involving Rad52 and other proteins like BRCA1 and PALB2 remain to be completely identified. Especially, some mutations in Rad52, including hRad52 S346X, may lower mutagenic effects to help to reduce the risk of breast cancer in BRCA1/2 mutation carriers. Though the long-term consequences of such therapies require more research, ongoing study of Rad52 inhibitors might offer a useful approach for treating BRCA-deficient tumors [11]. Especially in prostate and ovarian cancers, the important roles of homologous recombination (HR) and DNA mismatch repair (MMR) in cancer susceptibility. Correcting DNA replication mistakes requires MMR, and deficits in MSH2 and MSH6 mutations are associated to hereditary malignancies such Lynch syndrome and prostate cancer [12]. Particularly high-grade serous forms of ovarian cancer, around 20–25% of patients have pathogenic mutations in DNA repair genes such as BRCA1/2, greatly raising cancer risk. In mutation carriers, preventive treatments such bilateral salpingo-oophorectomy (BSO) can drastically lower this risk. Furthermore, influencing prostate cancer susceptibility are additional genetic elements like changes in ATM and CDK12 [13].

PHYTOCHEMICALS WITH ANTICANCER POTENTIAL

Managing these malignancies, guiding therapy options, especially the use of PARP inhibitors targeting HR-deficient tumors, depends on thorough genetic profiling. Through tailored therapeutic approaches, the changing knowledge of these genetic pathways is essential overall for enhancing patient outcomes. the evolution and effectiveness of PARP inhibitors in treating prostate and ovarian tumors especially. PARP inhibitors including olaparib niraparib and rucaparib excel at treating tumors that carry faults in BRCA1/2 genes but have different ways of working therapeutic breakdown and absorption profiles [14]. Major drug reactions include stomach issues, low blood cell counts, and fatigue with frequent nausea complaints. Studies demonstrate these inhibitors increase PFS rates in ovarian cancer patients so they receive maintenance therapy recommendations from multiple healthcare settings. Research proves that rucaparib and olaparib PARP inhibitors work best to treat prostate cancer especially for patients with precise genetic changes [15]. The book demonstrates how HR deficit and BRCA mutation testing

help achieve better medical results and explains how PARP inhibitors add to the performance of immune checkpoint inhibitors and other anti-cancer treatments. Our medical field needs to investigate how resistance develops against cancer drugs and how both inherited and damaged DNA impact cancer treatment [16].

While researchers have investigated the potential of plant extracts like *Urtica membranacea, Artemisia monosperma*, and *Origanum dayi*, further research is needed to identify the specific active components responsible for the anticancer effects. These plant extracts are complex mixtures of various phytochemicals and attributing the observed effects to the extract as a whole limits our understanding of the underlying mechanisms [17]. Isolating and characterizing the individual bioactive molecules within these extracts is crucial. Identifying the specific active compounds is essential for developing targeted therapies. Once the key molecules are identified, their structure-activity relationships can be investigated to optimize their efficacy and minimize potential side effects. This knowledge will pave the way for developing more potent and selective anticancer drugs derived from these natural sources [18].

PROSTATE CANCER RESPONSIBLE GENES

PCa stands as the second most common cancer among men worldwide and ranks as the fifth major cause of cancer deaths. The formation of cancer starts with damaged DNA and mutations that can occur either in body cells or throughout the genetic line affect your chances of developing PCa [19]. When DNA damage response systems fail to safeguard our genome they create cancer especially when BRCA mutations occur. Two genetic mutations called BRCA1 and BRCA2 affect how well HR repairs damage in DNA so the body needs different kinds of repair systems such as BER and NER to fix DNA whenever HR faces challenges [20]. When cancer cells fail to fix their DNA defects in BRCA-mutated tumors PARP inhibitors create synthetic lethality to destroy them. Medical standards recommend testing at-risk patients while helping doctors identify helpful genetic therapy options by studying their patient's genes [21]. Different treatment recommendations for different areas, however, show the need of standardized procedures in controlling BRCA-associated prostate cancer.

Due mostly to DNA damage, prostate cancer (PCa) shows notable genomic instability marked by amplifications, deletions, and chromosomal rearrangements [22]. Specifically BRCa1 and BRCa2, germline mutations in DNA damage response (DDR) genes have been linked to this instability. Nicolosi et al. found that 30.7% of 3,607 men with prostate cancer had germline mutations; other alterations included ATM and PALB2 [23]. With BRCA2 mutations associated to a worse prognosis, advanced metastatic cancer has a greater incidence of BRCA mutations than do original tumors. Damaged p53 and PTEN genes found in advanced tumor stages along with somatic mutations assist health professionals in understanding disease progression patterns [24]. The BRCA genes support DNA repair and gene activation yet their changes boost the chance of developing cancer. Breast and ovarian cancer mutation families benefit from genetic tests that help determine proper treatments and screening guidelines. Research studies TOPARP and PROFOUND demonstrate that cells with DDR mutations respond best to PARP inhibitors when used to treat advanced prostate cancer that has resisted hormone therapy [25]. Two additional ways PARP inhibitors develop resistance involve higher drug elimination from cells plus casual reversions in BRCA gene neighborhoods. Our research aims to develop better treatment strategies both by studying BRCA markers beyond DNA-repair differences and by making PARP inhibitors work better for personalized prostate cancer care [26].

Herbal medicine is becoming more and more important worldwide, especially in underdeveloped nations where it is the main healthcare resource because of the great expenses of modern medications. Treating illnesses, particularly cancer, the main cause of mortality globally, depends mostly on medicinal plants. With one in every 31 women expected to have breast cancer, rates of the illness are especially alarming in South Africa [27]. Although they have long employed several medicinal plants for cancer therapy, traditional healers in areas like the Eastern Cape still have mostly unrecorded information that is passed down orally [28]. Usually resulting from DNA mutations brought on by environmental elements, cancer affects 80–90% of instances and has been connected to such causes in study. Developing novel cancer medicines depends on medicinal plants as they provide complex molecular structures impossible to synthesis chemically. With proven great medicinal value, especially in traditional Indian medicine, neem (*Azadirachta indica*) epitribes this potential [29]. By causing death in cancer cells, increasing antioxidant activity, and strengthening the immune system, its active compounds—azadirachtins and nimocinol—show anticancer action. Studies show that neem can drastically lower tumor development in animal models and could improve the effectiveness of traditional therapies while lowering negative effects. Joining herbal medicine tradition with modern research methods helps us create better treatments and protect natural medical knowledge to fight more effectively against cancer [30].

BIOACTIVE PLANT EXTRACTS

The Ayurvedic plant *Tinospora cordifolia* or Giloy receives recognition for its various health benefits because it works as a tonic and anti-inflammatory agent while also boosting

sexual energy. According to tradition Giloy promotes long life by protecting against major diseases especially when taken as starch to treat both dysentery and chronic diarrhea [31]. Drinking Giloy juice helps defend against cancer development and supports cancer treatment while also treating skin conditions and relieving chronic fevers. Research needs more study yet evidence shows that berberine and tinosporin make *Tinospora cordifolia* helpful for cancer and radiation protection. Wheatgrass stands out for its substantial chlorophyll levels which align closely with human blood while also containing vital enzymes and amino acids that help cells stay healthy [32].

Through its content of abscisic acid and superoxide dismutase SOD the plant material breaks down cancer cell protection, so they become detectable by the immune system and produce better overall health [34,35]. Renowned for its medicinal qualities, aloe vera has more than 75 active components—mostly polysaccharides and glycoproteins—that cooperate to lower tumor load and boost immune response to cancer [33]. Finally, Ocimum sanctum, often known as Holy Basil, exhibits anticancer action especially against fibrosarcoma cells and is known for its great variety of active chemicals, including eugenol [34]. Tulsi's cytotoxic properties and ability to lower tumor volume in animal models have been demonstrated using extracts from the plant, therefore underscoring the significance of conventional medicinal herbs in contemporary therapeutic settings [35]. These plants taken together show the great possibilities of herbal treatments in treating cancer and enhancing health, thereby stressing the necessity of more study to combine conventional knowledge with contemporary scientific developments [36].

With forecasts of 26 million new cases and 17 million deaths by 2030, the International Agency for Research on Cancer predicts that in 2012 there were 14.1 million new cancer diagnoses and 8.2 million cancer deaths globally [37]. With about 60% of present cancer therapies come from natural items, especially plants, cancer remains a major worldwide health issue despite great progress. Well-known molecules include Taxus diterpenes and vinca alkaloids emphasize the plant world as a major source of anticancer drugs [38]. The effectiveness of plant-derived chemicals as inhibitors at different phases of carcinogenesis is attracting much more attention. With 10% to 40% of cancer therapies worldwide come from these sources, especially in Asia, research has found over 3,000 plants with purported anticancer characteristics [39]. With a varied spectrum of around 2,400 plant species, ethnobotanical study finds special possibilities. Three extracts *Urtica membranacea, Artemesia monosperma*, and *Origanum dayi* were selected for additional research after a recent study looked at seventeen whole plant extracts flora for their impact on human tumor cell lines [40]. These extracts reveal their possible efficacy as anticancer drugs as they showed dose-dependent cytotoxicity against several cancer cell lines while preserving healthy cells [41].

The study concentrated on the processes of cell death caused by these extracts and found that their anticancer effects were much influenced by apoptosis. One extract also exhibited encouraging effects in stopping tumor growth in an animal model of breast cancer, suggesting that entire plant extracts might be useful reagents in cancer treatment. Highlighting their possibilities for cancer treatment, the anticancer qualities of certain plant extracts are discussed [42]. After 24 hours, Extract 5 induced a 13% rise in the sub-G1 cell population, indicating apoptotic activity; Extract 11 greatly raised G2 phase cells without altering the sub-G1 population . Extract 10 revealed a significant drop in G1 phase cells and a 9.4% rise in the sub-G1 population. Furthermore evaluated was intracellular caspase-3 activity; Extract 5 caused a 3.2-fold rise following 24 hours, indicating death; Extract 10 also showed higher activity (1.8-fold). By comparison, Extract 11 had no appreciable effect on caspase-3 activity [43].

As Extract 5 triggered PARP cleavage and displayed DNA laddering, both suggestive of caspase-3-dependent death, further studies verified the death mechanisms of Extract 5. Additionally investigated was the expression of apoptotic proteins; Extract 5 dramatically raised Bax and Bik mRNA levels while lowering Bcl-2 mRNA levels. Extract 10 showed comparable effects; Extract 11 showed a distinct expression profile [44].

Systems biology approaches and multi-omics data offer powerful tools for building metabolic models of prostate cancer. However, the complexity of the disease requires even more comprehensive and dynamic models. Integrating diverse data sources, including genomics, transcriptomics, proteomics, and metabolomics, can provide a more holistic view of the metabolic alterations driving prostate cancer development and progression. Refining the metabolic models to incorporate spatial and temporal dynamics is crucial for understanding how these pathways interact and adapt over time and in different microenvironments. Such detailed models can help identify key regulatory nodes and potential therapeutic targets that may not be apparent from static models. Advanced computational techniques, including machine learning and artificial intelligence, can further enhance the predictive power of these models [45].

IN-VIVO INVESTIGATIONS

Significantly, in vivo investigations showed that Extract 5 significantly shrank tumor size in a mouse model of breast cancer, indicating its possible application as an anticancer therapy has future prospects [46]. These results suggest that entire plant extracts—especially from *Urtica membranacea, Artemisia monosperma*, and *Origanum dayi*—could provide

interesting paths for cancer treatment [47]. Especially in reducing drug resistance, their multi-target systems might have benefits over single molecules. To assess efficacy and safety in people and investigate the particular molecules within these extracts that support their anticancer activities, more in vivo investigations and clinical trials as well as other research is required. This all-encompassing strategy could help oncologists create successful natural remedies [48].

IN-SILICO ADVANCEMENTS

In silico analysis serves today as an essential computational method for studying bioactive compounds as they relate to prostate cancer gene metabolic pathways. The computational method makes use of superior algorithms and molecular modeling methods to estimate the effects of different phytochemicals upon biological pathways and genetic targets [49]. The research outcome of interaction prediction enables scientists to find therapeutic candidates in a faster and more resource-efficient way when compared to conventional laboratory testing methods. Predictive modeling enables safety and efficacy tests together with bioavailability evaluations during early stages which saves time and reduces costs in the drug discovery pipeline [50].

Modern bioinformatics and cheminformatics technologies help in silico tools improve their analysis of intricate prostate cancer metabolic pathways. These analytical methods establish simulations that trace how bioactive substances affect specific genetic targets which demonstrates their capacity to control cancer indicators [54]. The study of phytochemical binding to vital tumor-promoting receptors and enzymes remains possible through molecular docking analysis. Systems biology approaches utilize multiple omics data points including genomics and proteomics together with metabolomics to establish detailed prostate cancer metabolic models which lead to finding new therapeutic targets and biomarkers [52].

In silico analysis provides a valuable platform for preliminary screening and identification of potential therapeutic compounds. However, the true efficacy and safety of these compounds can only be established through rigorous in vivo studies and clinical trials. In vitro studies, while informative, cannot fully replicate the complex interactions within a living organism. Therefore, translating the promising results observed in silico into clinical settings requires extensive validation in animal models and subsequently in human trials [51].

Furthermore, clinical validation is essential to assess the long-term effects and potential side effects of these bioactive compounds. While initial studies may demonstrate promising short-term outcomes, long-term evaluation is crucial to determine the sustained impact on cancer control and the potential for adverse effects over extended periods. Clinical trials with diverse patient populations and long-term follow-up are necessary to establish the true clinical utility of these compounds [52].

The implementation of artificial intelligence alongside machine learning in in silico analysis produces exceptional predictive abilities to discover bioactive compounds with combined effects on prostate cancer treatment. These technologies have the ability to evaluate substantial datasets so they can detect hidden patterns among data points which standard methods would fail to see [53]. Research teams achieve better candidate selection through the integration of screening outcomes with simulated predictions. Through recent improvements in in silico analysis scientists gain speed in therapeutic agent discovery while creating prospects for personalizing prostate cancer treatment by targeting unique metabolic information and gene expressions [54].

CONCLUSION

The research studies the combination between in-silico bioactive compound analysis with genetic metabolic interactions that affect prostate cancer development. The frequency of prostate cancer occurs as the main malignancy affecting males because BRCA1 and BRCA2 mutations create genetic damage to DNA repair systems while increasing risk for aggressive disease forms. BRCA2 mutations raise PCa risk four times higher than other mutations do. The research demonstrates that mutations in tumors lead to positive reactions with DNA-damaging medications mainly PARP inhibitors through dysfunctional DNA repair system exploitation. This paper explores the combination opportunities between traditional herbal medicines and modern scientific approaches while studying anticancer properties of Neem and Giloy among other plants. Researchers use in-silico computational approaches to discover therapeutic compounds together with their genetic target bonds which enables creation of patient-specific treatment approaches. The inclusion of research-based natural compounds into clinical procedures would improve PCa treatment results yet ongoing studies must examine their actions in modern healthcare settings.

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