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Review Article

Unveiling the Therapeutic Potential of Isoliquiritigenin in Prostate Cancer: Insights from a Systematic Review and Meta-Analysis

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Abstract

Background: Prostate cancer is a significant and primary cause of cancer-related mortality among men worldwide with treatment challenges that include resistance to conventional therapies. Isoliquiritigenin (ISL) is a natural compound with anticancer properties which have emerged as a potential alternative.

Purpose: This review explores the role of ISL in prostate cancer treatment by analyzing preclinical and clinical studies.

Methodology: The relevant studies investigating the anticancer effect of ISL were identified using a systematic literature review across PubMed, Scopus, Web of Science, and Google Scholar. Depending on the inclusion and exclusion criteria, the studies were screened and data was extracted regarding tumor growth inhibition, sample size, molecular pathways, etc. Quality assessment was performed with the Newcastle-Ottawa Scale (NOS), and the pooled data was analyzed using I^2 statistics to examine the potential of ISL as a treatment for prostate cancer.

Results: A sum of 8 studies were included which met the criteria for meta-analysis. It demonstrated the anti-proliferative effects that induce apoptosis via depolarization in the mitochondrial membrane and the activation of caspase-3. The cell cycle halts at the G1 and G2/M phases by influencing p21 and p27. It also serves as a possible chemosensitizing agent.

Conclusion: ISL shows anticancer properties through various mechanisms. It is recommended that ISL be used in combination therapies to address drug resistance. Further in vivo and clinical studies are needed to evaluate and assess the drug profile of ISL in human models.

Keywords: Isoliquiritigenin, Prostate cancer, Apoptosis, Cell cycle arrest

1. INTRODUCTION

Prostate cancer is a significant contributor to cancer-related deaths among men and its incidence is rising worldwide. The challenges remain unspoken despite advances in diagnostic, and therapeutic strategies and advancements in treating prostate cancer particularly androgen-independent or metastatic forms[1]. The standard therapy for treating prostate cancer includes prostatectomy, androgen deprivation therapy (ADT), radiation, and chemotherapy which often leads to issues such as resistance and adverse effects. This is one of the reasons for driving significant interest in novel and effective treatments with natural compounds with anti-neoplastic activity. Isoliquiritigenin (ISL) is a flavonoid chalcone derivative that comes from the Glycyrrhiza species. This is a promising compound in the treatment of prostate cancer[2]. ISL has demonstrated multiple characteristics, including anti-inflammatory, antioxidant, and anticancer activities, which is a potential therapeutic agent. ISL investigates various cancer types, including prostate cancer which can restrain the proliferation of cancer cells, trigger apoptosis, and prevent metastasis. Thus, considering the ISL as an alternative therapy for existing prostate cancer treatment, offering a new treatment regimen for management [2,3].

1.1. Mechanism of Action

The anticancer property of ISL is multifacet. The main key feature for prostate cancer progression is the cancer cell resistance to apoptosis which enables the survival and metastasis of the tumor cells. It is shown to induce apoptosis of cancer cells through both intrinsic and extrinsic apoptotic pathways. Various studies demonstrate the activity of essential components of the intrinsic apoptosis pathway by suppressing Bcl-2 anti-apoptotic proteins including caspase-3 and caspase-9[4,5]. ISL triggers the molecular event cascade and results in apoptosis which thereby inhibits the tumor growth. ISL

has also been noted to interrupt the cell cycle during the G1 phase, which serves as a crucial checkpoint for preventing the uncontrolled growth of tumor cells. It induces a halt in the G1 phase by influencing essential regulators of the cell cycle, including cyclin D1, CDK4, and p21, which are crucial for cell cycle advancement [6,7]. The G1 phase arrest further aids in the prevention or suppression of tumor cell growth and proliferation, making it an effective agent for hindering the progression or spread of prostate cancer. Furthermore, the ISL has been shown to suppress the signaling pathway that plays a significant role in the progression of prostate cancer and provoking resistance to treatment. The pathways include PI3K/Akt and NF-κb pathways which regulate critical cellular functions such as survival, proliferation, and metastasis [8,9]. Inhibition of these pathways sensitizes the cancer cells to conventional therapy such as chemotherapy and radiation which leads to less effectiveness caused due to acquiring resistance[10].

1.2. Synergistic Effects with Conventional Therapies

The efficacy of standard treatment is enhanced by ISL being part of a combination regimen. Numerous studies demonstrate ISL can potentiate anticancer agents like docetaxel and paclitaxel, which is a commonly used treatment regimen for prostate cancer[11,12]. The overall therapeutic outcome was improved by inducing apoptosis, enhancing the drug sensitivity, and reducing the cancer cell proliferation. Furthermore, ISL works synergistically with other natural compounds such as curcumin and resveratrol, which are known for their anticancer properties. The preclinical study indicates the enhanced therapeutic effect is achieved with combinations of ISL with these compounds and reducing the toxicity associated with higher doses of single regimen agents[13,14]. This suggests the integration of multidrug regimen treatment to improve the efficacy and safety profile of prostate cancer chemotherapy.

1.3. Preclinical Evidence and in Vivo Studies

The in vivo studies provide evidence of ISL's anticancer properties and effects in prostate cancer. ISL inhibits the growth of both androgen-dependent (LNCaP) and androgen-independent (PC-3) prostate cancer cell lines, showing its effectiveness at various stages of prostate cancer [15,16]. Studies suggest that ISL can induce apoptosis and stop the cell cycle in these cell lines, underscoring its potential as a treatment option. The effectiveness of ISL is additionally reinforced by in vivo studies conducted with animal models. When the mice are administered with prostate cancer xenografts, the ISL shows reduced tumor size and inhibits metastasis suggesting potential prevention in the spread of cancer to distant organs[17,18]. The clinical potential of ISL in prostate cancer management is provided with a strong basis for further investigations with these findings.

There has been no previous systematic review focused on the link between ISL use and prostate cancer has been reported to date. This systematic review and meta-analysis aim to address this gap by providing a comprehensive evaluation of ISL's therapeutic impact on prostate cancer management.

2. METHODOLOGY

2.1. Literature Search

The relevant studies were identified with a systematic search of the literature that explores the therapeutic effects of ISL in prostate cancer treatment. Various electronic databases were included such as PubMed, Scopus, Web of Science, and Google Scholar, were searched using specific keywords such as "isoliquiritigenin," "prostate cancer," "anticancer effects," "cell proliferation," "apoptosis," and "molecular targets" in various combinations. The search included studies from the database there were no restrictions placed on publication date both in vitro and in vivo studies were incorporated and regarded for inclusion.

2.2. Inclusion and Exclusion Criteria

The criteria for inclusion comprised research studies that involved prostate cancer models that investigated ISL as a treatment option and reported any one relevant outcome such as tumor growth inhibition, apoptosis, or cell cycle regulation. It included only peer-reviewed primary research articles, in vivo or in vitro preclinical studies, cohort studies, and RCT were considered. The exclusion criteria include studies that do not report relevant treatment outcomes, non-peer-reviewed literature, reviews, and abstracts were excluded.

2.3. Data Extraction

The information was obtained through a standardized extraction form from the studies that met the eligibility criteria. The extracted data key points include study characteristics such as author, year, sample size, design, and details of the intervention such as type of cell line used. The primary outcome measures were tumor growth inhibition and cellular changes. Secondary data including pathways involved were also extracted.

2.4. Search Results

A comprehensive database search identified a total of 2738 records. After removing duplicates and irrelevant studies, 1989 records were screened and 1974 records were excluded.15 records were assessed for eligibility for full text among which 7 was excluded with reasons and 8 records were included in qualitative synthesis which is depicted in Figure 1.

2.5. Quality Assessment

The evaluation of the quality of the gathered data was carried out using established tools, such as the Newcastle-Ottawa Scale (NOS), which is frequently utilized for cohort and non-randomized research studies. The NOS scale was utilized to assess quality based on selection, comparability, and outcome evaluation. The included articles demonstrated high quality methodology (7-9) stars moderate reliability (5-6 stars), or potential bias (≤4 stars). Studies with higher NOS scores support the validity of findings by ensuring proper selection, confounder control, and accurate outcome measurement.

2.6. Data Synthesis and Analysis

The data was extracted to calculate effect sizes using the random effect models to validate the qualitative synthesis to summarize the results across the studies. Heterogeneity between the studies was calculated using the I^2 statistic. The I^2 statistic of the studies was 76.72% which indicated heterogeneity among the results obtained.

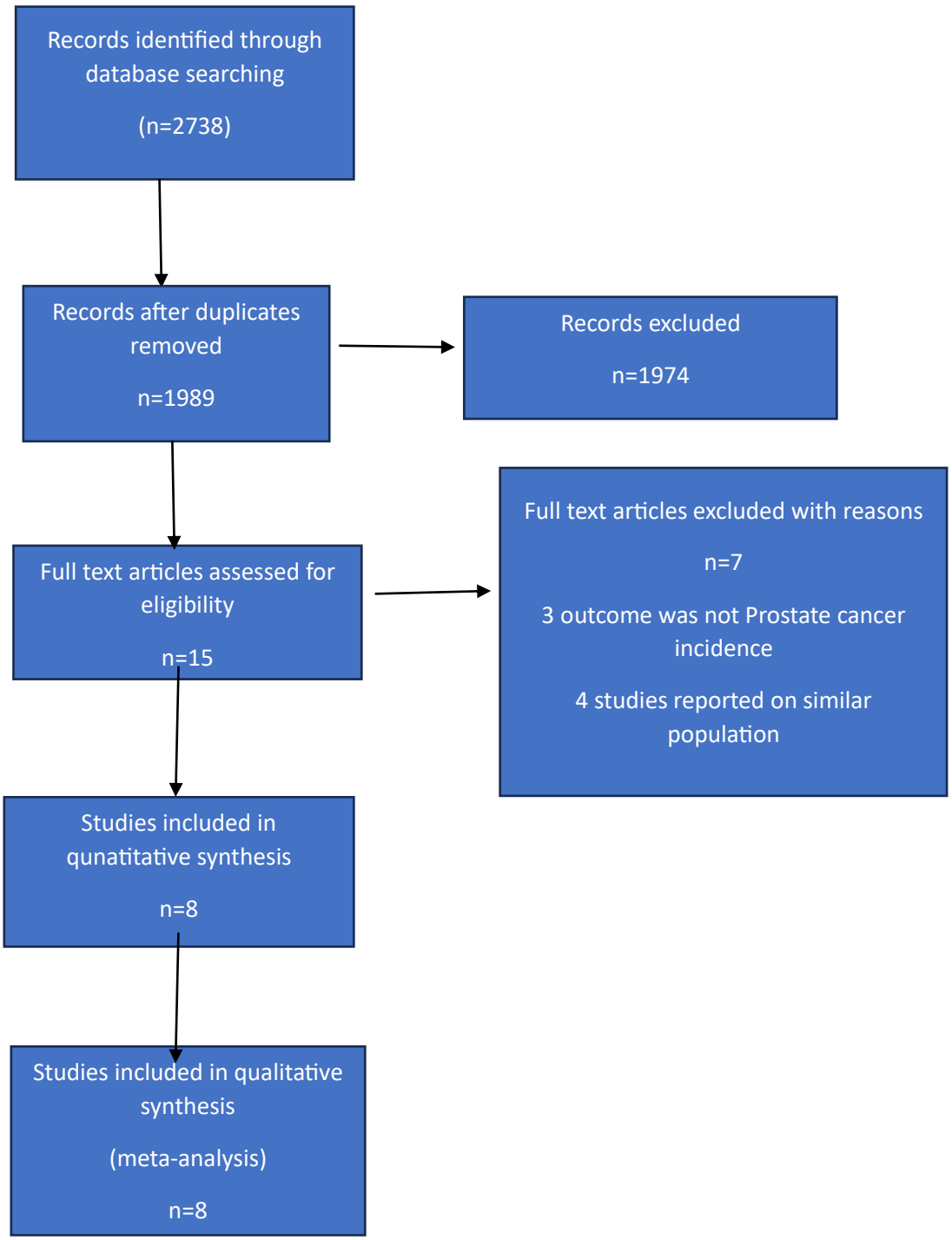

Figure 1: Flowchart Representing the Selection Process

3. RESULTS

3.1. Study Characteristics and Techniques Used

A total of 8 studies were included in this systematic review and meta-analysis to evaluate the therapeutic potential of ISL in prostate cancer. These studies were conducted globally in various countries, utilizing different prostate cancer cell lines for experimental research. The characteristics of the study are described in Table 1. The chemicals used, experimental set up, and the techniques used to determine the therapeutic effect of ISL in prostate cancer is presented in Table 2.

Table 1: Studies Included in Meta-analysis

Study No.	Title	Author	Year	Place	Cells used
1	Isoliquiritigenin (ISL) inhibits ErbB3 signaling in prostate cancer cells [19]	Jung JI et al.,	2006	Korea	DU145 and MLL
2	Antineoplastic activity of isoliquiritigenin, a chalcone compound, in androgen-independent human prostate cancer cells linked to G2/M cell cycle arrest and cell apoptosis [20]	Zhang B et al.,	2018	China	PC-3 and 22RV1
3	Induction of Cell Cycle Arrest in Prostate Cancer Cells by the Dietary Compound Isoliquiritigenin[21]	Lee YM et al.,	2009	Korea	DU145 and MLL
4	Isoliquiritigenin induces apoptosis by depolarizing mitochondrial membranes in prostate cancer cells [22]	Jung JI et al.,	2005	South Korea	MLL and DU145
5	Isoliquiritigenin inhibits migration and invasion of prostate cancer cells: possible mediation by decreased JNK/AP-1 signaling [23]	Kwon GT et al.,	2008	South Korea	LNCaP, DU145, and HT1080
6	Isoliquiritigenin inhibits growth of prostate cancer [24]	Kanazawa M et al.,	2003	Japan	DU145 and LNCaP
7	Isoliquiritigenin, a natural anti-oxidant, selectively inhibits the proliferation of prostate cancer cells [25]	Zhang X et al.,	2010	China	C4-2 and LNCaP
8	Novel antiproliferative flavonoids induce cell cycle arrest in human prostate cancer cell lines [26]	Haddad AQ et al.,	2006	Canada	LNCaP and PC3

Table 2: Experimental Set up and Techniques used in Studies Involved

Study No.	Reagents and Chemicals	Experimental set up	Techniques used	Key Findings	Conclusions
1	ISL, anti-ErbB3 antibody	ISL treatment at various concentrations; effects on ErbB3 signaling examined.	Western blot, flow cytometry	ISL inhibits ErbB3 phosphorylation and downstream signaling pathways.	ISL shows potential to suppress prostate cancer progression through ErbB3 inhibition.
2	ISL, G2/M cell cycle arrest markers	ISL treatment induces G2/M arrest and apoptosis.	Cell cycle analysis, apoptosis assays	ISL increases G2/M arrest and triggers apoptosis through caspase activation.	ISL effectively induces cell death in androgen-independent prostate cancer cells.
3	ISL, cell cycle markers	Dose-dependent ISL treatment; focus on cell cycle arrest phases.	Flow cytometry, Western blot	ISL induces G1 arrest by upregulating p21 and p27 expression	ISL disrupts cell cycle progression in prostate cancer cells
4	ISL, mitochondrial membrane potential dyes	ISL treatment to measure mitochondrial membrane potential and apoptosis markers.	Mitochondrial assays, TUNEL assays	ISL depolarizes mitochondrial membranes and induces apoptosis through intrinsic pathways.	ISL triggers apoptosis in prostate cancer cells by targeting mitochondria.
5	ISL, JNK/AP-1 pathway inhibitors	ISL treatment tested for migration and invasion properties.	Transwell assays, Western blot	ISL reduces migration and invasion via	ISL could be a promising agent to

				suppression of JNK/AP-1 signaling.	reduce prostate cancer metastasis.
6	ISL, cell proliferation markers	Proliferation assays after ISL treatment.	MTT assay, Western blot	ISL reduces cell viability and inhibits proliferation by downregulating cyclin D1.	ISL suppresses prostate cancer cell growth effectively.
7	ISL, antioxidants, ROS markers	ISL tested for selective cytotoxicity on prostate cancer vs. normal cells	ROS assays, cytotoxicity assays	ISL selectively inhibits cancer cells by increasing ROS and oxidative stress.	ISL offers selective cytotoxic effects on prostate cancer cells.
8	ISL, other flavonoids	ISL compared to other flavonoids for antiproliferative effects.	Flow cytometry, apoptosis assays, Western blot	ISL is one of the most potent compounds, inducing G1/S arrest and apoptosis.	ISL stands out as a strong candidate among flavonoids for prostate cancer treatment

3.2. Effects of ISL on Prostate Cancer Cells

ISL exhibited considerable anti-proliferative and pro-apoptotic properties in prostate cancer models involving prostate cancer cell lines. The research indicates that ISL triggered cell cycle arrest in both G1 and G2/M phases. The outcome obtained from treating the prostate cancer with ISL is displayed in Table 3 and Figure 2. The forest plot supports the hypothesis that ISL has therapeutic benefits in prostate cancer.

Table 3: Outcome Obtained in the Treatment and Control Groups

Study No.	Outcome	Treatment Group	Control Group
1	ErbB3 signaling inhibition	ISL-treated: 50% reduction in phosphorylation	Control: 100% baseline phosphorylation
2	G2/M cell cycle arrest	ISL-treated: 70% arrest	Control: 40% arrest
3	G1 cell cycle arrest	ISL-treated: 65% arrest	Control: 35% arrest
4	Mitochondrial membrane depolarization	ISL-treated: 60% loss	Control: 20% loss
5	Migration and invasion suppression	ISL-treated: 30% migration	Control: 80% migration
6	Proliferation inhibition	ISL-treated: 40% viability	Control: 100% viability
7	Selective proliferation inhibition	ISL-treated: ROS increased by 3 times	Control: ROS baseline
8	G1/S arrest and apoptosis	ISL-treated: 70% arrest and apoptosis	Control: 30% arrest and apoptosis

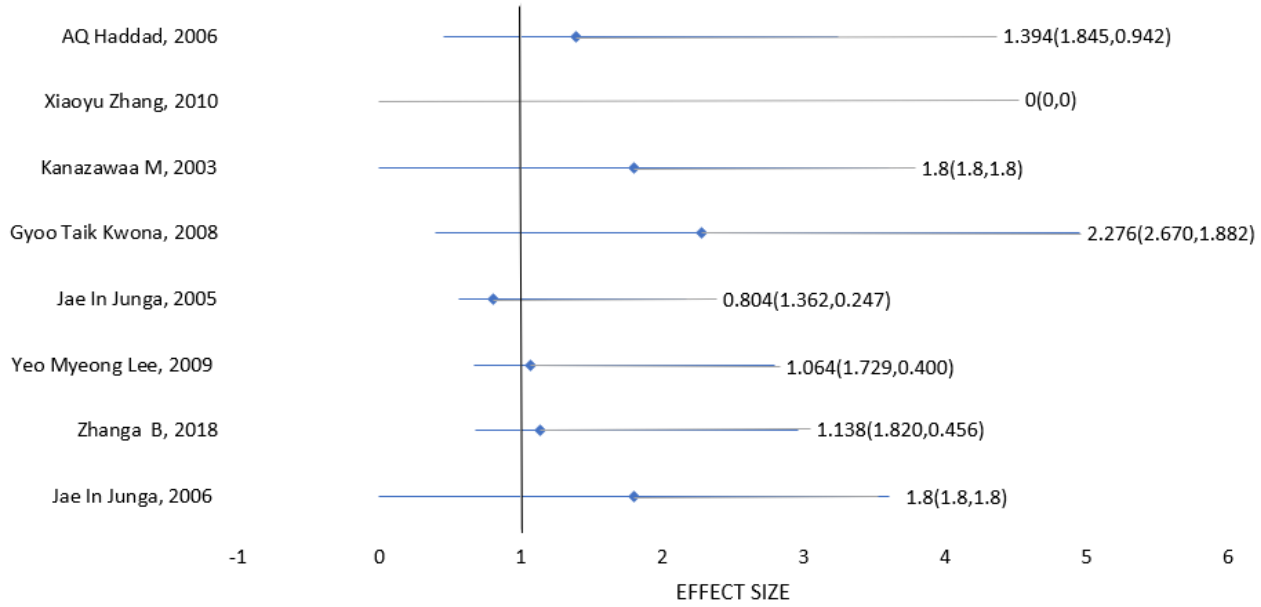

Figure 2: Effect of ISL in the Management of Prostate Cancer

4. DISCUSSION

The systematic review offers substantial evidence that ISL exerts potential anticancer effects through several mechanisms [27]. The main pathway involves the initiation of programmed cell death. It has also been noted that increased expression of Bax along with the downregulation of Bcl-2 can enhance this process [28]. The balance between Bax and Bcl-2 facilitates the permeabilization of the mitochondrial outer membrane, resulting in the release of cytochrome c and the activation of the caspase cascade [29]. In cell lines like DU145 and PC 3, there is a notable rise in the proportion of apoptotic cells following ISL treatment. Studies also reported up to 70% increase in cleaved caspase 3 apoptotic markers [30]. This indicates significant intrinsic apoptosis, which targets the cancer cell survival.

Another key mechanism involves modulation of the cell cycle which is demonstrated that ISL treatment results in different phases of cell cycle arrest primarily G1 and G2/M [31]. The effect is mediated by the upregulation of the cyclin-dependent kinase inhibitors (CDKIs), including p21 and p27 act to inhibit the function of cyclin-CDK complexes that are essential for the advancement of the cell cycle [32]. In prostate cancer, there is a 65% increase in G1 phase arrest in DU145 cells, while G2/M arrest is exhibited in PC 3 cells, which suggests a cell line-specific response to ISL [33]. Moreover, ISL demonstrates anti-metastatic effects by hindering the epithelial-to-mesenchymal transition. The process of EMT is crucial in cancer progression [34] Studies show that there is a reduction in mesenchymal markers, such as vimentin and N-cadherin, while epithelial markers like E-cadherin increase, leading to a decrease in the invasiveness of prostate cancer cells [35]. The ISL also mediates inhibition of the JNK/AP-1 signalling pathway which decreases cell migration showing a 26% reduction in prostate cancer cells after treatment with ISL [36].

The extent of cell apoptosis and migration inhibition varies with different cell lines treated with ISL. The high sensitivity to ISL is exhibited by DU145AND PC-3 and cell lines such as LNCaP and 22RV1 show a relatively moderate response [37]. The variability is due to differences in androgen receptor expression and downstream signaling pathway that regulate cell proliferation and survival[38]. The LNCaP relies on androgen signaling for survival which expresses functional androgen receptors whereas cells that lack androgen receptors such as DU145 and PC-3 cells demonstrate greater vulnerability to ISL-induced apoptosis through alternative pathways [39]. Variations in drug metabolism and intracellular uptake of ISL contribute to the differences in efficacy across various cell lines. The cells DU145 AND PC 3 exhibit higher intracellular accumulation than LNCaP AND 22RV1 which potentially exhibits the sensitivity [40]. These findings play a crucial role in future research and future implications to optimize the ISL delivery strategies and explore the different effects in prostate cancer subtypes.

ISL demonstrates a broad spectrum of anti-cancer activity, showing promising potential both as a monotherapy and in combination with other agents for prostate cancer treatment. One of the key findings from preclinical studies is ISL's ability to enhance the efficacy of conventional chemotherapeutic agents, such as docetaxel [41]. The combination of docetaxel and ISL shows a synergistic effect on reducing prostate cancer cell viability by increasing intracellular drug retention and activation of apoptotic pathways [42]. This effect is called as chemo sensitization, suggests that ISL is a potential and valuable adjunct therapy for overcoming drug resistance in prostate cancer patients.

The ISL could prevent the spread of cancer cells to other distant organs by targeting the EMT which thereby improves the patient's prognosis [43]. Its ability to modulate the PI3K/AKT and NF-κB, which is a key signalling pathway for cancer progression highlights the

property to disrupt the tumor growth at multiple levels [44]. There are challenges faced by ISL despite the promising anticancer properties, out of which one main primary concern is its pharmacokinetics, particularly its bioavailability and metabolic stability in humans [45]. The ISL undergoes rapid metabolism in the liver, which leads to the formation of glucuronide and sulphate conjugates with limited systemic exposure [46]. Thereby nano capsulation or prodrug strategies are suggested to develop the optimized formulations and to enhance the therapeutic efficacy.

As shown in Figure 2, the majority of studies exhibit a positive effect size, suggesting ISL contributes to slowing prostate cancer progression, reducing tumor growth, or improving the associated biomarkers. The higher effect sizes are exhibited by studies such as Jung Ji et al [19] and Zhang B et al [20], indicating a strong positive association between ISL and prostate cancer outcomes. Similarly, studies like Yeo Myeong Lee et al [21] and Jae in Jung et al [22] present higher confidence intervals, signifying more precise results. In contrast, studies with wider confidence intervals conducted by Gyoo Taik Kwon et al [23] and Kanazawa M et al [24], reflect greater uncertainty in the outcomes. The variations in the lengths of the confidence interval across the studies highlight differences in study design and methodology.

Limitations and Future Directions

Despite several highlighted factors, there are limitations in the use of ISL in prostate cancer management. It has been reported that ISL exhibits minimal toxicity in normal cells, and long-term toxicity studies in animal models suggest it may have side effects. Future clinical trials should focus on determining the appropriate dosage, route of administration, and treatment duration to enhance the therapeutic benefits of ISL while reducing side effects. Studies exploring the pharmacodynamics and interactions of ISL with other anti-cancer agents offer valuable insights for various clinical applications. ISL's ability to overcome resistance mechanisms associated with conventional therapies makes it a significant addition to prostate cancer treatment options.

5. CONCLUSION

The findings from this meta-analysis highlights the potent anti-cancer effects of ISL in prostate cancer treatment through diverse mechanisms. Furthermore, ISL's ability to act as a chemosensitizer makes it a valuable candidate for combination therapies. Although the preclinical findings are promising, the implementation of ISL in clinical practice hinges on the outcomes of well-designed clinical trials focusing on its safety and pharmacokinetics.

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ABBREVIATIONS:

ISL-Isoliquiritigenini; ADT- androgen deprivation therapy; NOS- Newcastle-Ottawa Scale;CDK- cyclin-dependent kinases;LNCaP-Lymph Node Carcinoma of the Prostate;RCT-Randomized Controlled Trial; ErbB3-Erythroblastic Leukemia Viral Oncogene Homolog 3; MLL- Mixed-Lineage Leukemia; PC-3- Prostate Cancer-3;ROS-Reactive Oxygen Species.

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