Comparative Analysis of Anti-Proliferative Effect of *Zingiber Officinale (Ginger)* and *Solanum Lycopersicum (Tomatoes)* on Testosterone-Induced Benign Prostatic Hyperplasia in Male Albino Rats.

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***Abstract*: Benign Prostatic Hyperplasia (BPH) is a debilitating condition that enlarges the prostate and surrounding tissues mostly in men in their 50's. This inflammatory process can lead to uncontrolled passage of urine, incomplete urine flow, dribbling at the end of urine stream, hematuria and inability to ejaculate. Zingiber officinale (Zo) and Solanum lycopersicum (Sl) are known to have anti-proliferative, anti-oxidant, and anti-inflammatory effect on the prostate. A completely randomized experimental design was used for this study. A comparative analysis of the two plant extracts were carried out against the standard drug dutasteride (Brand name: Tamsudart) on male albino rats for 30 days. The animals were grouped into six. Analysis of Prostate Specific Antigen, C-reactive protein, Serum electrolytes, and stress markers such as malondialdehyde were assayed, and the prostate weight checked. The positive control group were slightly elevated $p<0.05$, the standard drug and Zingiber officinale (Zo) extract group had a significant reduction of tumour, while the Solanum lycopersicum (Sl) group was not significant. The cocktail group of 100mg Zo and 100mg Sl were effective in reducing prostate size. The combination of the two plants as a cocktail gave a synergistic effect in reducing prostate size but singly Zo had a better outcome than Sl. This study is tailored towards averting surgical procedures like open prostatectomy and Trans urethral resection of the prostate with attendant complications. The study is therefore of immense health care and economic benefit to especially third world nations where poverty, health care facilities and human resource are grossly inadequate or completely absent as evident in this post-pandemic era.**

***Key words*: Benign Prostatic Hyperplasia, Anti-proliferative, anti-inflammatory, Zingiber officinale, Solanum lycopersicum.**

I. INTRODUCTION

Benign Prostatic Hyperplasia (BPH) is an inflammation of the prostate and areas surrounding it. It is one of the most common urinary diseases affecting men, generally after the age of 50 (Csikos *et al*., 2021). Benign Prostatic Hyperplasia is a prevalent disease with significant health and economic impacts on patients and health organisations across the world, whilst the cause/initiation of the disease process has still not been fully determined. It is estimated to affect about 50-61% of the men population as they age due to unregulated hyperplastic growth of the epithelial and fibromuscular tissues of the transition zone and periurethral area. (Devlin et al., 2021). The mortality rates arising from prostate hyperplasia forms like prostate cancer has also risen to 3.8% globally. A recent study has put the lifetime prevalence worldwide at 26.2%, with no statistically significant change in this rate over the last 20 years (Lee et al.,2017)

BPH has been found to have a multifactorial origin, maybe as a result of normal condition of aging, due to changes in male sex hormone, inflammation, cytokine, chemokine effects, 5-alpha reductase activity etc. Inflammation can lead to generation of reactive oxygen species; activation of autoimmune T cells which has been found to increase prostate cells since the prostate is an immune competent tissue (Madersbacher *et al;* 2019). Prostate Specific Antigen (PSA) > 4ng/l have been used to depict BPH and it increases as the prostate size and volume enlarges. Recently, even higher values are seen in asymptomatic cases so its non-specificity has led to measuring the speed at which the prostate size increases and free PSA levels (Thomson *et a*l; 2003).

High consumption of fruits and vegetables have been known to have anti-inflammatory and anti-cancer effects and generally enables the body to fight diseases, hence it impacts a state of general wellbeing. The roles of Zingiber officinale (Zo) or ginger and Solanum lycopersicum (Sl) or tomatoes on testosterone induced BPH using male albino Wistar rats is determined in this study. Zingiber officinale (Zo) or ginger has been known to display anti-inflammatory, anti-oxidant and anti-proliferative activities, this has shown its role as a chemopreventive agent. (Prasanthi *et al*; 2012). It has been shown to exhibit anti-proliferative effect on tissues, research by (Obisike *et al*; 2020); showed anti-inflammatory, anti-oxidant and suppressive effects of ginger on BPH induced male Wistar rats.

Similarly, many studies have associated the consumption of tomatoes and tomato products with a reduced risk of prostate cancer (Etminan *et al*; 2004). The hypothesis is that lycopene, the main carotenoid in tomatoes, has a direct effect on the prostate. Growing data shows that tomatoes may contain other carotenoids that inhibit prostate carcinogenesis. The amount of lycopene in fresh tomatoes depends on their variety, ripeness levels and environmental conditions under which it was grown. Cooked or even industrialized tomatoes have been shown to have more bioavailable lycopene because the cell wall is broken and the lycopenes extracted from the chloroplasts. (Edinger *et al*., 2006). Tomatoes, use mechanisms like antioxidant function, inhibition of cell cycle progression and increased apoptotic index in prevention of prostate hyperplasia (Wertz et al., 2004).

The use of drugs has been found to be efficacious in the treatment of BPH, however they are associated with adverse effects; ranging from impotence, gynaecomastia, orthostatic hypotension, to abnormal ejaculation amongst others. Also, surgical interventions are usually initiated as a treatment strategy, however, the cost and risks e.g., hematuria, (damage to nearby organs), associated with it excludes it as a routine treatment (Kalu *et al.*,2016, Eleazu *et al.*, 2017). The trend then is increased search for alternative methods of managing this disease using natural remedies, hence this study.

II. MATERIALS AND METHODS

A completely randomised trial was used for this study. Thirty male albino Wistar rats weighing 180g-260g were bought from Benue State University animal house. They were randomly shared into fives and housed. The experimental animals were allowed to acclimatize to the laboratory conditions for 10days as per the Organisation for Economic Co-operation and Development (OECD) guidelines. The animals were housed in cages under standard husbandry condition (at temperature. of 26+/-2^{0}C relative humidity of 45-55% and alternate cycle of 12hours of dark and light with free access to commercial pellet laboratory diet and water ad libitum throughout the experimental period. All the procedures in the experiment were carried out according to the Guide for the Care and Use of Laboratory Animals set by Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). At the end of the experiment, the animals were sacrificed by cardiac puncture under anaesthesia.

Sample collection and Preparation.

Fresh Zingiber officinale (ginger) and Solanum lycopersicum (tomatoes) were obtained from Nyanya market in Abuja Municipal Area Council, Nigeria. The plants were identified by a Taxonomist at the Herbarium section, Department of Plant Science and Biotechnology, Faculty of Natural and Applied Sciences, Nasarawa State University, Keffi, Nasarawa State, Nigeria.

Purchase of Drugs and Chemicals.

The BPH drug Dutasteride (Tamsudart) and testosterone propionate induction drug was gotten from a pharmacy in Utako, Abuja after explaining the need for the drug. Analytical grade ethanol was used for plant extraction.

Preparation of Crude Extract.

Z. officinale and S. lycopersicum extracts were prepared in the Central Research Laboratory of the Biochemistry and Molecular Biology Department, Nasarawa State University, Keffi. The ginger rhizome and tomato fruits were sliced and air-dried at ambient temperature for two weeks, after which they were pulverized to uniform powder using an aluminium electronic blender. The dried and powdered ginger rhizome and tomato fruits (350g each) was extracted using ethanol and the Soxlet apparatus. The solvent was allowed to evaporate using a rotary evaporator and dried in an oven at 40^{0}C. The dried extract was used for the study.

Methods

Induction of Benign Prostatic Hyperplasia

Testosterone propionate (brand name Testost by Laborate Pharmaceuticals India) was gotten from Klen Pharmacy in Abuja, Nigeria. 4mg/kg/body weight of Testosterone propionate was injected intramuscularly to induce Benign Prostate Hyperplasia (BPH) for eight days. Prostate Specific Antigen (PSA) was analysed on two rats from induced groups to confirm BPH (Obisike *et al.*, 2020).

Experimental design After ten days of acclimatization, the rats were weighed and randomly divided into six groups (five rats per group) as follows: All groups were induced except the normal or control group.

Group 1: Normal Group (Non induced, non-treated) n=5
Group 2: Positive Control (Induced and not treated) n=5
Group 3: Standard Group (Dutasteride 0.01mg/ml) n=5
Group 4: Zingiber officinale extract (ZE) 200mg/ml n=5
Group 5: Solanum lycopersicum extract (SE) 200mg/ml n=5
Group 6: Combination of 100mg/ml ZE + 100mg/ml SE n=5

The weights of the rats were recorded weekly. The study lasted for 30days (10 days acclimatization, 8days induction and 12days of treatment).

Sample Collection and Storage

Blood was collected in plain bottles and allowed to clot for biochemical analysis. Biochemical analysis was performed on serum obtained after centrifugation of whole blood from three animals from each group. The blood was put in plain containers without anticoagulant and spun at 2500rpm for 5mins. Standardized diagnostic kits (Spectrum biotechnologies UK) were used for spectrophotometric analysis (Microlife, 990) and determination of the following biochemical parameters: Serum electrolytes (Sodium,

potassium, chloride, bicarbonate) urea and creatinine (renal function test), Prostate Specific Antigen (PSA), Transforming Growth Factor b (TGF-b) and C - reactive protein (CRP).

Biochemical analysis

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Haematological assay

The blood samples were collected into EDTA sample bottles for determination of the complete blood cell count which included red cell count, packed cell volume (PCV), haemoglobin concentration (Hb), platelet count (PLT), Erythrocyte indices, total white blood cell counts and its differentials using Automated Haematology Analyzer (Hemax 330 haematology analyser).

Histopathological analysis

The prostate and liver were harvested, sectioned and processed by a pathologist in FMC, Keffi.

Statistical Analysis.

Analysis using Statistical Package for the Social Sciences (SPSS) Version 23 was carried out. All analysed results were presented as mean +/- SD. One-way analysis of Variance (ANOVA) or Friedman Test was used where appropriate. Differences in mean were considered statistically significant when $p < 0.05$.

III. RESULTS AND DISCUSSION

Results

Haematological parameters.

The effects of the extracts on some haematological parameters in prostate induced rats are displayed in table 1. There was significant ($p<0.05$) decrease in RBC in groups 3 and 4 compared to the control. HGB was significantly lower in group 4 and significantly higher in group 6. This is an indication for good blood level control to prevent anaemia. MCHC increased significantly in group 3 and decreased in group 6. For MCH, the values also decreased significantly in groups 2, 5 and 6 compared to the control. MCV decreased significantly in group 4 and increased significantly in group 6. Significant decrease of HCT was noticed in groups 3 and 4 while PLT counts were significantly higher in group 3 compared to the control this might be an indication for a good bleeding disorder count.

Table 1: Haematological parameters

GROUP	RBC	HGB	MCHC	MCH	MCV	HCT	PLT
Group 1(NC)	5.30±0.47^a	14.10±1.80^a	44.00±1.78^a	26.66±2.25^a	59.33±2.06^a	32.00±3.57^a	247.00±162.43^a
Group 2(PC)	5.30±1.33^a	13.43±2.32^a	44.33±7.17^a	26.00±3.22^b	58.33±1.03^a	31.33±8.11^a	168.00±5.86^a
Group 3(STD)	4.90 ±0.35^b	13.80±0.70^a	48.00±2.68^b	28.00±0.89^a	58.66±1.86^a	28.66±2.73^b	301.66±42.57^b
Group 4(Zo)	4.73±0.13^b	12.36±0.75^b	45.66 ±2.25^a	26.33±1.03^a	57.66±0.51^b	27.33±.51^b	237.00±18.61^a
Group 5(Sl)	5.33 ±0.27^a	13.83±0.80^a	44.33±.516^a	26.00±0.00^b	58.00±0.00^a	31.00±1.78^a	192.0±61.135^a
Group 6(Z+S)	5.73±0.20^a	14.33±1.13^c	41.66±1.03^c	24.00±0.00^b	59.66±1.03^b	34.33±2.06^c	197.33±53.18^a

Keys: RBC- Red blood cell count, MCH- Mean cell haemoglobin, MCHC-Mean cell haemoglobin count, MCV- Mean Cell Volume, HCT-haematocrit, HGB-haemoglobin, PLT-Platelet count NC- Negative control (Non induced, non-treated), PC- Positive control (Induced and not treated), STD- Standard drug (Dutasteride group), Zo (Zingiber officinale group), Sl (Solanum lycopersicum group).

Proteins and Body weight.

Table 2 is the results of CRP, PSA, TGF-b, Testosterone and body weight. The results showed significantly low concentration of C - reactive protein (CRP) in groups 1, 3 and 4 compared to the positive control. CRP is an acute-phase protein that is produced in high quantities in inflammatory states. However, there were no significant changes observed on the levels of PSA. For Transforming Growth factor-b (TGF-b), the values were significantly higher across all the experimental groups compared to the control. Testosterone level was also significantly higher in group 2 compared to the control. There were no significant changes in body weights observed across all the test groups compared to the control.

Table 2: Proteins and Body weight (PSA, TGF-b-ng/ml, Testo-mg/dl, Wt-kg)

GROUP	CRP (mg/dl)	PSA	TGF-b	Testo	Wt
Group 1	4.00±0.00^a	0.17±.19^a	0.57±1.78^a	1.70±0.28^a	242.46±15.87^a
Group 2	8.66±3.61^b	0.41±.19^a	0.99±7.17^b	2.67 ±1.18^b	239.83±24.52^a
Group 3	5.66±.51^b	0.36±.38^a	0.93±2.68^c	1.66±0.70^a	235.700±16.54^a
Group 4	6.00±.89^b	0.30±.20^a	0.80±2.25^c	1.41±0.42^a	232.80±24.39^a
Group 5	8.33±2.87^a	0.443±.04^a	0.81±.516^c	1.61±0.50^a	238.03±15.45^a
Group 6	9.33±4.41^a	0.34±.30^a	0.82±1.03	1.37±0.12^a	245.06±8.15^a

Keys: Prostate Specific Antigen (PSA), Transforming Growth Factor b (TGF-b) and C - reactive protein (CRP), Testo - Testosterone and Wt - body weight

Kidney function biomarkers

The effects of the extract on some kidney function indices in prostate induced rats is as shown in table 3: The outcome showed significantly lower total protein concentration in groups' 4 and 5 compared to the control. There were no significant changes observed in urea concentration across all the test groups. Creatinine level was significantly higher in group 4 and lower in group 5 compared to the control. There was significant decreased of Uric acid in group 2 and 4 but increased in group 5 compared to the control.

Table 3: Kidney function biomarkers (Total protein(mmol/l) Urea(mg/dl), Creatinine(umol/l), Uric acid (mg/dl)

GROUP	T. PROT	Urea	Creatinine	Uric acid
Group 1	6.54±1.87[a]	91.15±17.76[a]	1.52±.53[a]	10.28±.35[a]
Group 2	6.01±.10[a]	71.92±4.43[a]	2.27±.03[a]	8.96±.31[b]
Group 3	6.43±.50[a]	88.46±32.05[a]	2.36±1.14[a]	10.23±.57[a]
Group 4	5.07±1.75[b]	85.51±6.39[a]	2.98±1.13[b]	8.21±.64[b]
Group 5	10.08±1.69[c]	94.10±17.91[a]	0.83±.08[c]	11.47±.92[c]
Group 6	7.11±.59[a]	93.20±26.92[a]	1.74±.61[a]	10.20±1.57[a]

Key: T. PROT - Total protein

Serum Electrolytes(mmol/l)

The results of electrolytes concentration as presented in figure 1: shows a significantly high concentration of sodium ion compared to the control. Potassium ion significantly decreased in groups 3 and 4 but a significant increase was observed in group 5. Similarly, there was a significant increase of chloride ion in group 5, increase of bicarbonate ion in group 6 but a decrease in group 2 compared to the control respectively.

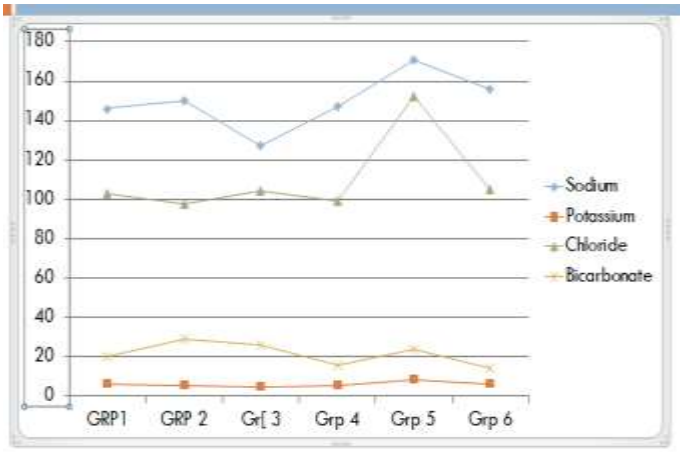

Fig 1: Serum electrolyte graph

Organ analysis (kU/l)

Figure 2: is the result of organ analysis of Kidney homogenate protein (KID-PROT), superoxide dismutase (SOD), catalase (CAT), malondialdehyde (MDA) and reduced glutathione (GSH). Results showed a significant increase in total protein concentration in group 5 compared to control. There was a significant reduction of SOD in group 5(Sl group). CAT significantly increased in group 3, a better antioxidant effect of CAT was observed in groups 4 and 6. While there was a significant increase of MDA in group 2 and GSH significantly increased in group 5.

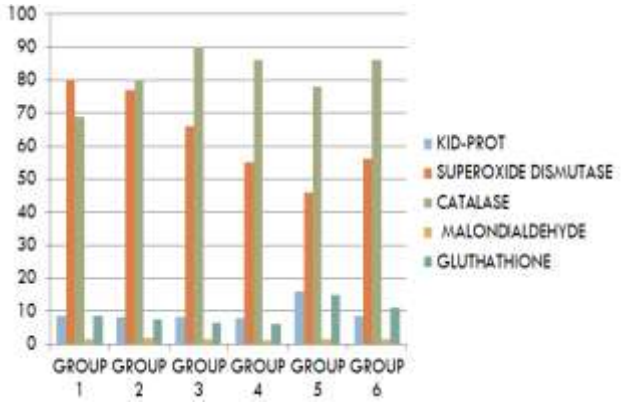

Figure 2: Organ analysis (kU/l)

Histopathological sections of the prostrate

Figure 3: shows the histopathological sections of the prostrate. The group 2 show hyperplasia of the prostate tissue against the control group 1. Groups 3 and 4 showed reduced lobular extension same with the combo groups of Group 6. (Transforming Growth factor beta, TGF-b), a growth factor is a proliferative index found to be higher in Group 2, the non-treated group.

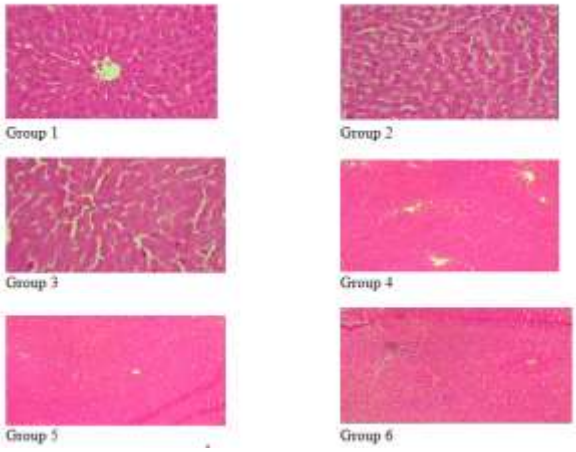

Figure 3: Histopathological sections of the prostrate

IV. DISCUSSION

In this study, our findings show an increase in haemoglobin level in Group 6, where better carriage of oxygen by cells was observed, against Groups 1 and 2, implying that monitoring of blood levels is paramount in BPH to prevent anaemia in the elderly which can be deleterious. A meta-analysis by Eleazu et al., (2017) suggested constant monitoring to avoid inhibitory action by the 5-alpha reductase enzyme on red cell production. PSA and CRP should also be monitored alongside as observed in study, where values were higher than those of standard drug groups.

The outcome of Zo was observed to be better, indicative of antiproliferative and anti-inflammatory response. This is in agreement with the work of Kalu et al., (2016) and Eleazu et al., (2017) who reported that Zo has antiproliferative and antioxidant effect on cells. Ginger is one of the most commonly consumed dietary condiments in the world. The oily resin from the rhizomes contain may bioactive components like gingerol (1-4,hydroxyl-3-methoxyphenyl-5-hydroxy-3-decanone) which is the primary pungent ingredient that is believed to exert a variety of remarkable pharmacological and physiological activities (Surh et al.,1999 and Obisike et al., 2020). This report also aligns with previous investigations who demonstrated that dry ginger powder or solvent extracts of ginger roots induced cell cycle arrest and apoptosis in skin, breast, prostate, colon and ovarian cancer cells (Shukla et al., 2007).

Though total protein was quite high in Grp 5 against the control, but was however better in Groups 4 and 6. This might provide a better option or solution for renal function control**.** The significant reduction in prostate weight and Prostate Specific Antigen as shown in our study agrees with the report of Obisike et al., (2020) on the assessment of antiproliferative effect of Zo. The combo group of Zo and Sl had a better effect than Sl signifying maybe a synergistic effect between the two plants and the richness of plants in resolving disease process caused by aging or oxidative processes. Superoxide dismutase (SOD) an anti-oxidant enzyme which reduces the production of reactive oxygen species (ROS) and protects against oxidative damage was observed to be reduced in Group 5, against the control and an increase in Grp 4. This could make Zo a better anti-inflammatory indicator. Similarly, serum electrolyte analysis showed a better effect in groups 3,4 and 6, this might be as a result of challenging androgenic transformation of testosterone to dihydrotestosterone which is said to increase with ageing in men (Devlin et al.,2021).

Malonaldehyde (MDA) a physiological keto-aldehyde produced by lipid peroxidation of unsaturated lipid, is a secondary product of lipid peroxidation, and is used as an indicator of free radical tissue damage (Ohkawa et al., 1979, Ugwu et al., 2019). As a biomarker of oxidative stress and lipid peroxidation it causes tissue damage and many health problems e.g., cancer, psychiatry, chronic obstructive pulmonary disease, asthma or cardiovascular disease. Increase in free radicals cause overproduction of MDA. In advancing ages, the oxidative stress increases and may aggravate many pathological conditions including BPH. In this study, the stress marker MDA, was not significant in Grp 4 as the anti-oxidant effect of Zo was peaking up, it was however higher in groups 5 and 6 showing a better effect than Sl group.

Catalase (CAT), similarly catalyzes the breakdown of hydrogen peroxide to water and oxygen; and is a very important enzyme that protects cell from oxidative damage by reactive oxygen species. Our findings showed a significant increase of CAT in group 3, but a better antioxidant effect was observed in groups 4 and 6. SOD, Catalase and glutathione(GSH) were decreased significantly in BPH control groups using Zo and the combination group generally more than the Sl group, this suggests that these enzymes play vital antioxidant role in protecting cells from oxidative stress in line with *Ocimum gratissimum* extract study on BPH rats (Ugwu et al.,2018).

Circulating antioxidant enzymes may be used up in an attempt to counter the enhanced lipid peroxidation in the affected tissue (Barker et al., 1997). With the decrease of antioxidants in BPH, an accumulation of free radicals such as OH^{o} might occur. These highly reactive oxidant molecules oxidize DNA, lipids and proteins and it reacts with nearby structures. Any oxidative lesion that is not repaired may lead to mutations, increasing the risk of damaging tissues (Cooke et al., 2000). This enhanced lipid peroxidation occurs as consequence of the insufficient power of depleted antioxidant defense system for a prolonged duration. In addition, it has been suggested that antioxidants have protective role against BPH as well as progressive prostate cancer (Sikka 2003). So, treatment with Zo and Sl (though singly, Zo did better) reversed the effect caused by oxidative stress from BPH as shown by the increase of the endogenous antioxidants. Suggestive that this might be helpful as a natural alternative for managing BPH. Several investigations have shown that ginger have anti-proliferative effect in colorectal carcinoma and fractions of dried extract of Zo rich in polyphenols reduced proliferation in gastric adenocarcinoma cells (Sakulnarmrat et al; 2015). This is also evident in this study where there is evident reduction in proliferation of prostate cells.

There was proliferation in the basal epithelia of the control groups, this data agrees with the analysis by Devlin (2021) where luminal and basal epithelial hyperplasia were seen, mostly in the basal region and more differentiated luminal epithelial. In vitro, this process occurred via growth factor expression from mesenchymal cells acting on luminal cells in a paracrine fashion. Thus, in BPH, mesenchymal-induced stem cells may be recruited to the prostate by basal and luminal progenitors under the influence of growth factors, resulting in proliferation of both or either of the stromal and epithelial cell layers.

Zo effect on cells is compared to that of Prasanthi et al., (2012), who suggests that Zo has a chemo-preventive effect on cells. Sl stops cancer cell proliferation or rather inhibits cell cycle progression in various cell carcionoma types

(Edinger et al., 2015), though this was not observed in this study, however, a combo with Zo gave good outcome. These results show an anti-proliferative, anti-oxidant effect of Zo on parameters more than Sl. Their combined effect gave a better resolution of effects both physically and at cellular level. The anti-oxidant and anti-proliferative effect of Zo is better seen in the organ analysis depicting its effectiveness in reducing reactive oxygen species that can degenerate to various disease processes. BPH progression can be reduced or inhibited by the use of Zo, and a combination of Zo and Sl can also be effective in reducing BPH. Their accessibility and affordability therefore make them a better option aside the presence of the polyphenols like gingerols, paradols, shogoals and essential oils present in the plant found to give good effects.

Pathway of anti-proliferative mechanisms of ginger.

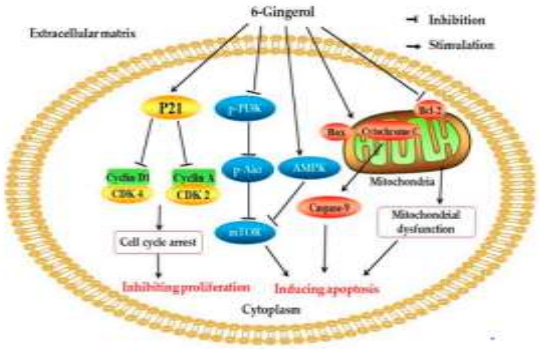

Figure 4

Figure 4: Several signalling pathways are involved in the anti-proliferative mechanisms of ginger (6-gingerol, one of the bioactive compounds). CDK- Cyclin-dependent kinase; P13K: Phosphoinositide 3-kinase; AKT: Protein kinaseB; mTOR: Mammalian target of rapamycin; AMPK: 5' adenosine monophosphate-activated protein kinase; Bax: Bcl 2-associated X protein; Bcl-2: B-cell lymphoma2 (Mao et al; 2019).

Effect of Zo and Sl on BPH

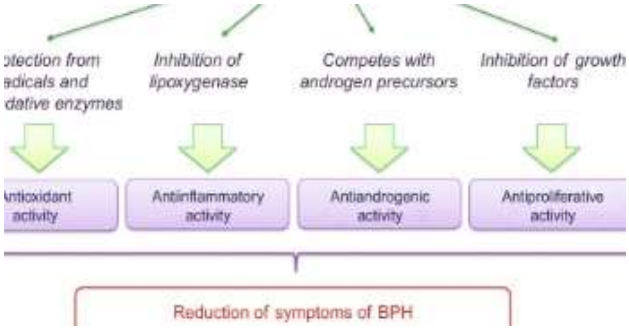

Figure 5: Overall effect of Zo, Sl: (Giuseppe et al., 2018)

V. CONCLUSION

Good healthy and feeding habit is encouraged. Exercise is necessary to reduce the deteriorative effects of aging. The use of natural products like Zo and Sl is encouraged for consumption in varied forms. Our men folk should use more Zo and go for regular checkups to monitor their biochemical and hematological parameters for better health. Due to limited resources and technology, molecular profiling was not done. Further studies on the molecular profiling of BPH and a trial of these extracts on human subjects are advocated.

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Conflict of Interest.

No conflict of interest whether financial or otherwise expressed amongst the researchers.

Author Contribution

Each author contributed in varied significant parts towards the success of this research work.

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