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Role of Vitamin C and Citrus Fruits on Urinary Tract Infections in Owerri, Imo State of Nigeria

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Abstract
Complementary and alternative medicine has been recognized as an effective approach for the treatment of urinary tract infections by antibiotic-resistant bacteria. This experimental descriptive study assessed the role of Vitamin C and Citrus fruits on Urinary Tract Infections in Owerri. A total of 384 participants comprising men and women residing in Owerri, ranging from 18 to 70 years were selected using random sampling technique. The data were collected using self-structured interview questionnaire as well as the experimental results, and were analyzed using simple percentages and Odds Ratio. Out of 384 participants, 126(32.8%) of them had urinary tract infections, 26.3% males were infected, while, 39.2% of the females had infections. Of the 107 participants who were consuming Vitamin C and Citrus fruits, 92.5% (OR=3.8) of them had no bacterial infection growth; out of 90 participants of those on Vitamin C alone, 77.8%(OR=2.4) had no infection, as 60.0%(OR=1.8) of those on fruits alone had no infection, while, those without Vitamin C and Citrus fruits had the highest growth infection rate of 65.5%. The result revealed sharp differences in the rate of prevention of growths of infection among the four groups of the participants. The data analysis, showed that there was statistical significance (p=0.05) in the rate of prevention of urinary tract infection growth rates among the four groups. It is pertinent, to create more awareness among the population in the locality and indeed in the general populace on the importance of Vitamin C and Citrus fruits.
Keywords: *Bacteria, Antibiotics, Alternative-medicine, Resistance, Prevention, Prevalence.*

INTRODUCTION
Urinary Tract Infection (UTI) is the invasion and presence of bacteria or any other pathogen in any part of urinary system (Redd,2002, Ana *et al*., 2015), posing severe public health problems. It is caused by a range of pathogens, but most commonly by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterococcus faecalis* and *Staphylococcus saprophyticus* (Ana *et al*.,2015) and are most common outpatient infections with a lifetime incidence of 50-60% in adult women (Martha et al.,2019, Kasper *et al*., 2018). Among the uropathogens, *Escherichia coli* is the most common bacteria (75-90%) in both the community and hospital infections, where as other pathogenic bacteria such as *Proteus mirabilis, Staphylococcus saprophyticus, Enterococcus faecalis Klebsiella pneumoniae and Pseudomonas aeruginosa* each are less (Sheerin and Glover,2019; Sheerin, 2011, Kasper *et al*., 2018). Nonetheless, Okoroiwu, 2008, in his study''Comparative study of urinary tract and reproductive tract infections in Niger Delta States, Nigeria'' posited that *Staphylococcus saprophyticus* is more common(13.8%) than *Escherichia coli* (10.9%).

In the management and treatment of UTIs, several types of antibiotics have been used for the purpose, and antibiotic therapy is an effective approach and reduces the duration of symptoms. Empirical treatment is usually within 5 days to 7 days of antibiotics and achieves a cure in about 85-90% of women. This type of regimen is equivalent to longer regimens and is more effective than a single dose administration (Sheerin and Glover, 2019, Asadi *et al*., 2019).

However, in the last decades, the extensive use of antibiotics has resulted in the emergence of antibiotic-resistance bacterial pathogens and leads to the spread of antibiotic resistance. Moreover, because of the chronic nature of UTIs and the potential for antibiotic resistance, a promising approach to prevention and treatment is favourable, and recently, various approaches have been developed to overcome the problems associated with antibiotic resistance (Khameneh *et al*., 2019; 2016; 2019). In that pursuance, complementary and alternative-medicine has been recognized as an effective approach for the treatment of infection by antibiotic-resistant bacteria (Khameneh *et al*., 2019; Bazzaz *et al*., 2019;

Fazly *et al.,* 2018, 2016). This consists of a wide range of products like natural compounds, dietary supplements as vitamins and minerals and as well as probiotics (Baker *et al*., 2018). In addition, as governments hasten to formulate policies and protocols to regulate the sale and use of antibiotics, particularly in developing countries, there is also a need to look at alternative therapeutic modalities that can help control the pandemic of antimicrobial resistance (Verghese *et al*., 2018).

Vitamin C (Ascorbic acid) was identified in the early twentieth century in the search for a substance, the deficiency of which would cause scurvy (Hermila, 2017; Carpenter, 1986) and Scurvy was associated with Pneumonia in the early literature, which implies that the factor that cured scurvy might also have an effect on Pneumonia. Vitamin C is an antioxidant and any effects of Vitamin C may be most prominent under conditions when oxidative stress is elevated. Many infections lead to the activation of phagocytes, which release oxidizing agents referred to as reactive oxygen species (ROS), these play a role in the processes that lead to the deactivation of viruses and the killing of bacteria (Segal,2005). However, many of the ROS appear to be harmful to the host cells, and in some cases they seem to play a role in the pathogenesis of the infections (Akaike, 2001; Peterlians, 1997). This substance is an efficient water-soluble antioxidant and may protect host cells against the actions of ROS released by phagocytes. It is cheap, easily available and has few or no adverse effects and frequently prescribed as a nutritional supplement, it has established antioxidant effects and has even been used as an adjuvant in cancer chemotherapy.

Increased ROS production during the immune response to pathogens can explain the decrease in Vitamin C levels seen in several infections, there is evidence that plasma , leukocyte and urinary Vitamin C levels decrease in the common cold and in other infections(Hemila, 2017). The decrease in Vitamin C levels during various infections imply that, the Vitamin C administration might have a treatment effect on many patients with infections (Hume and Weyers, 1973).

Ever since Szent-Gyorgi recognized Vitamin C in citrus as the cure for scurvy in 1932, numerous studies have been carried out to elucidate its various biological properties (Svirbely and Szent-Gyorgy, 1932). Currently, ascorbic acid and citrus(fruits) are the most widely used supplements in the world (Naidu,2003). Increased Vitamin C levels are said to reduce the risk of arthritis, asthma, cataracts, periodontal disease, and stroke (Ge *et al*., 2008). All the known biological functions of Vitamin C originate from its chemical property as a reducing agent. It plays an important role in the maintenance of collagen, thus playing a critical role in wound repair and healing. Ascorbic acid is a cofactor in the conversion of dopamine to norepinephrine, is involved in the synthesis of catecholamines, catalyses enzymatic reactions necessary for the activity of certain hormones (Naidu, 2003). Moreover, its role in mitigating oxidative injury, restoring microcirculating flow and boosting antibacterial defense seems to promote recovery in patients with sepsis, burns, and multiorgan dysfunction (Oudemans-van *et al*., 2014).

Using of vitamins such as Vitamin C, trace elements and/or sugars is an effective approach in preventing UTs, and a combination of them shows positive results (Bibi *et al*., 2021) and Vitamin C, according to Ochoba *et al*., (2007), said that Vitamin C intake in pregnant women at a daily dose of 100mg has been able to prevent bacteriuria and UTI significantly, while, Mina *et al*., (2020) posited that Vitamin C serves as a safe treatment potential prophylactic agent in post Kidney transplantation UTI. The inhibitory impact of Vitamin C on the growth of some pathogens such as Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia and Staphylococcus saprophyticus has also been shown in some studies (Verghese *et al*., 2017; Carlson *et al*., 2001). The growing rate of antibiotic resistance in urinary tract pathogens has led to the search for non-antibiotic prophylaxis which is not affected by antibiotic resistance (Beerepoot and Geerling, 2016), and this is the focus of this study.

The evidence so far, for the effect of Vitamin C in reducing UTI episodes has remained inconsistent and has not been effective enough to be recommended as UTI prophylaxis, therefore, this study is aimed at providing the evidence based data on the effectiveness of Vitamin C and Citrus fruits on UTI causative agents, in order to create more awareness on useful usage of Vitamin C and citrus fruits for prevention of UTI or otherwise.

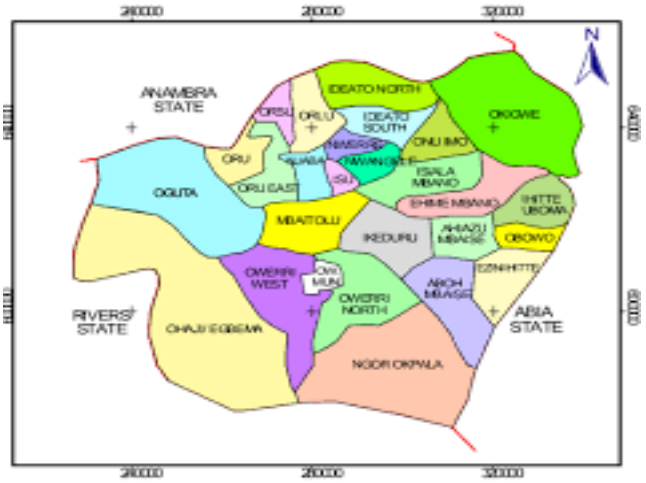
MATERIALS AND METHOD

Study Area

Owerri is the capital of Imo State in Nigeria, with three Local Government Areas (LGAs); Municipal, North and West, and has an estimated population (predominantly Christian) of about 1,401,873, as of 2016, and is approximately 100 square kilometres (40 sq miles) in area. The city is bordered by the Otamiri river to the east and the Nworie river to the south and has an airport 23 kilometres (14 miles) southeast of the city located in Obiangwu, Ngor Okpala LGA. Owerri sits in the rain forest and produce many agricultural products such as yams, cassava taro, corn, rubber and palm products.

According to the Köppen-Geiger system, Owerri has a tropical wet climate. Rain falls for most months of the year with a brief dry season.

The harmattan affects the city in the early periods of the dry season and is noticeably less pronounced than in other cities in Nigeria. The average temperature is 26.4°C. The city is home to many tertiary institutions including Imo State University, Federal University of Technology, Federal Polytechnic and others.



Map of Imo State showing the study area (Owerri and its environs-Municipal, Owerri West, Owerri North)

Study Design

This is an experimental descriptive study to assess the role of Vitamin C and Citrus fruits on etiological agents of Urinary Tract Infections among the inhabitants of Owerri, the Imo State capital.

Study Population

The study population consist of 384 men and women residing in Owerri and its environs, who agreed to be part of the study and who have not taken antibiotics for the past 5 to 6 months and are either taking Vitamin C as well as fruits (Oranges, Apple, Guava, Pineapple, Mango, Papaya(Pawpaw).

Criteria

Those who are within the age brackets of 18-70 years, have not taking antibiotic treatment for the past 5 to 6 months, resident, schooling, working or doing business within the three LGAs that make up Owerri.

Sample Size Determination

The sample size of 384 was determined using the sample size formula for simple proportion according to Naing et al.,2006, given as : $n = N^2 P(1-P)/d^2$, where n = sample size; N = 1.96 (Statistical constant); P = 50%(0.5) adopted because there was no similar study previously conducted in the area, and d = margin of error of 5% (0.05) , this gave a calculated sample size of 384.

Sampling Technique

The participants were recruited randomly until the sample size of 384 was obtained. They were recruited at both health facilities and communities.

Data Collection

A structured questionnaire was interviewer-administered to each of the participants to obtain information on socio-demographic characteristics and on when they had antibiotic treatment last, how often they take Vitamin C, Fruits and type (Oranges, Apple, Guava, Pineapple, Mango, Papaya(Pawpaw).

Sample Collection

Participants were provided with commercially sterile plastic containers labeled with identifiers such as name, age, sex, and date to collect about 5.0mls of Urine for urine culture. Written instruction was given on how to collect without contaminating the sample to avoid getting a wrong result.

Ethical Clearance

Ethical clearance for the this was granted by the Research Ethical Committee of National Open University of Nigeria. While, oral informed consent was obtained from the study participants. The purpose of the study, procedures, possible risks and benefits, rights and responsibilities of participants including the right to withdraw from the study at any time were described.

Laboratory Analysis

About 2.0mls of the urine samples were each centrifuged and examined under microscope using X10 and X40 objectives for pyuria before culture. The uncentrifuged samples were cultured with standard loop after mixing, on two media namely; CLED (Cystein Lactose Electrolyte Deficient) and MacConkey agar, incubated overnight at 37^0C for 24 to 48 hours, and the colonies(a single colony is accepted to represent one colony forming unit(CFU) were counted and identified using standard methods(physical appearance; biochemical methods, staining methods)

Statistical Analysis

Data were analyzed using simple percentages and Odds Ratio. The level of Significance was set at $p < 0.05$.

RESULTS

A total of 384 participants comprising 190 males and 194 females of the ages ranging from 18 to 70 years,

were enrolled into the study. Of these, 126 (32.8%) had Urinary Tract Infections (UTIs), while 258 representing 67.2% were negative. The etiological agents discovered were Escherichia coli, Staphylococcus saprophyticus, Klebsiella species, Serratia species. 26.3% of the males had UTIs while 39.2% of the females were infected (table 1). Table 2 is the age-related prevalence of UTIs of the participants. Age-groups of 61-70 years (50.0%) had the highest prevalence of infections, while, ages between 41-50 years and 51-60 years had 38.3% and 42.9% respectively,31-40 years and 21-30 years had prevalences of 25.8% and 24.6% each, while, the age -group of 18-20 had the lowest infection rate of 17.6% (Table 2). Table 3 is the Odds ratio analysis of the effect of Vitamin C and fruits on the etiological agents of UTIs which showed that Vitamin C, when combined with fruits in daily diets, highly prevented urinary tract infections (OR=3.8; growths=7.5%; no growths=92.5%) among the participants, Vitamin C alone prevented infection at ''no-growth'' rate of 77.8%(OR=2.4; growth=32.2%), Fruits alone prevented UTI at ''no-growth'' rate of 58.3% (OR=1.8; growth rate=41.7%). However, in those who were not taking either Vitamin C or fruits, urinary tract infections remain high (OR=0.8; growths=65.5%; no-growth=34.5%).

Table 1: Gender-related prevalence of UTI among the study population

Gender	No. Screened	No. Positive (%)	No. Negative (%)
Male	190	50 (26.3)	140 (73.7)
Female	194	76 (39.2)	118 (60.8)
Total	384	126 (32.8)	258 (67.2)

Table 2: Age-related prevalence of UTI among the study population

Gender	No. Screened	No. Positive (%)	No. Negative (%)
18-20	68	12 (17.6)	56 (82.4)
21-30	65	16 (24.6)	49 (75.4)
31-40	66	17 (25.8)	49 (74.2)
41-50	60	23 (38.3)	37 (61.7)
51-60	63	27 (42.9)	36 (57.1)
61-70	62	31 (50.0)	31 (50.0)
Total	384	126 (32.8)	258 (67.2)

Table 3: Prevalence of UTI among those taking Vitamin C; fruits (oranges, apple, guava, pineapple, mango, pawpaw)

Subjects	No. Screened	No. Positive (%)	No. Negative (%)	OR
Without Vit.C & Fruits	84	55 (65.5)	29 (34.5)	0.8
With Vit.C only	90	20 (32.2)	70 (77.8)	2.4
With Vit.C&Fruits	107	8 (7.5)	99 (92.5)	3.8
With Fruits only	103	43 (41.7)	60 (58.3)	1.8

Table 3 is the Odds ratio analysis of the effect of Vitamin C and fruits on the UTIs etiological agents showed that Vitamin C when combined with fruits highly prevented UTIs at ''no-growth'' rate of 92.5%. Vitamin alone prevented UTI at ''no-growth'' rate of 77.8%.

DISCUSSION

Urinary Tract Infections are severe public health problems and are caused by a range of pathogens, but most commonly by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterococcus faecalis* and *Staphylococcus saprophyticus* (Ana *et al.*, 2015), and are most common outpatient infections with a lifetime incidence of 50-60% in adult women (Martha *et al.*, 2019, Kasper *et al.*, 2018). The result of this study has buttressed previous surveys (Sheerin and Clover, 2019; Kasper *et al.*, 2018; Storm *et al.*, 2019, Okoroiwu, 2018 and Sheerin, 2008), who opined that UTI is caused by various etiological agents including, E.coli, Staphylococcus saprophyticus, Proteus mirabilis, Klebsiella species and others, and Vitamin C, when mixed with fruits in diets or taking singly have various degrees of relative antibiotic activities on etiological agents of urinary tract infections. In this study, the Odds ratio analysis of the effect of Vitamin C and fruits on the etiological agents of UTIs, showed that Vitamin C, when combined with fruits in daily diets, highly prevented urinary tract infections (OR=3.8; no growths=92.5%) among the participants, while, Vitamin C alone prevented infection at ''no-growth'' rate of 77.8% (OR=2.4; growth=32.2%), moreso, Fruits alone prevented UTI at ''no-growth'' rate of 58.3% (OR=1.8; growth rate=41.7%). However, the result noted that in those who were not taking either Vitamin C or fruits, urinary tract infections remain high (OR=0.8; growths=65.5%; no-growth=34.5%). This has laid credence to the statement that using of Vitamin C, trace elements and/or sugars is an effective approach in preventing UTIs and a combination of them gives positive results (Bibi *et al.*, 2021). In addition, Vitamin C according to Ochoba *et al.*, (2007), revealed that Vitamin C intake in pregnant women at a daily dose of 100mg has been able to prevent bacteriemia and UTI

significantly. In supporting the outcome of this survey, Mina *et al*., (2020), posited that Vitamin C serves as a safe treatment potential prophylactic agent in post kidney transplantation UTI. Some other studies, have reported inhibitory effect of Vitamin C on the growth of some UTI pathogens such as E.coli, Pseudomonas aeruginosa, Klebsiella pneumonia and Staphylococcus saprophyticus (Verghese et al.,2017, Carlson *et al*., 2001). And all these, can be evidenced by the fact that complementory and alternative medicine has been recognized as an effective approach for the treatment of infection by antibiotic-resistant bacteria (Khameneh et al., 2019; Bazzaz *et al*., 2019 and Fazhy *et al*., 2018).

A number of researches have demonstrated the inhibitory effects of Vitamin C on bacterial diseases, for instance, the inhibitory effect was demonstrated in vivo by a decrease in H.pylori gastric colonization in Mongolian gerbils that were administered Vitamin C orally for 7 days, moreover, epidemiological evidence seems to suggest that the decline in the incidence of gastric carcinoma, and P.pylori seropositivity prevalence might be linked to the consumption of Vitamin C supplements by 40% of the U.S population (Zhang *et al*., 1997). Furthermore, El-Gebaly et al., showed that Vitamin C had an inhibitory effect on the growth of *E. coli, Klebsiella* species, Citrobacter species, Enterobacter species, Proteus species and Pseudomonas species and said that the effect was consistent irrespective of the susceptibility pattern on the tested isolates (El-Gebaly *et al*., 2012).
Various explanations for the inhibitory effect of Vitamin C have been offered; a structural change in bacteria, such as irregularly constricted cells observed by phase contrast microscopy (Zhang *et al*., 1997), or elongated cells with disorganized membranes seen under the scanning electron microscope (El-Gebaly *et al*., 2012). The inhibitory effect of Vitamin C on bacterial biofilms may be due its anti-quorum sensing activity (Novak and Fratamico,2004). Other explanations include the presence of antioxidants, flavonoids, and phenolics in Vitamin C (Biswas *et al*., 2013), or the ability to lower the pH (El-Gebaly, 2012), as observed when Vitamin C intake consistently produced acidic urine in subjects (Habash *et al*., 1999. The lowered pH might account for the enhanced activity of antibiotics such as levofloxacin (El-Gebaly,2012) and azithromycin (Biswas *et al*., 2013). However, our report showed heavy and more growths among participants who were neither taking Vitamin C nor fruits and this further corroborated the evidence that Vitamin C and fruits have some antibiotic properties that must have prevented or inhibited these pathogens from growing or regenerating from those who consumed Vitamin C and fruits (Beerepoot and Geerling, 2016; Hermila, 2017) . Therefore, Vitamin C and fruits should be part of dietary supplements as suggested by Bakar, *et al*., (2018,) as it is believed, Vitamin C is an antioxidant and any effect of Vitamin C may be most prominent under conditions when oxidative stress is elevated and many infections lead to the activation of phagocytes, which release oxidizing agents referred to as Reactive Oxygen Species (ROS) as they play role in the processes that lead to the deactivation of viruses and the killing of bacteria (Segal, 2005).

In conclusion, this study has shown that Vitamin C when combined with fruits in diet or consumed alone has a profound preventive or inhibitory effect on the causative agents of urinary tract infections. It is therefore, advised that people should make use of Vitamin C and fruits especially citrus fruits part of their daily diets. Nevertheless, further studies are encouraged to look into dosage and quantity of fruits that can be consumed in a day to avoid over dose if any.

CONFLICT OF INTEREST: There is no conflict of interest between Authors.

AUTHORS' CONTRIBUTION:
The Idea/Concept: was by Dr Gideon.I.Okoroiwu

Data collection: by Dr Gideon.I.Okoroiwu and Dr Nwanganga Ihuoma Ubosi

Analysis: by Dr Nwanganga Ihuoma Ubosi

Original draft: by Dr Gideon.I.Okoroiwu and Dr Nwanganga Ihuoma Ubosi

Review and editing: by Dr Gideon.I.Okoroiwu and Dr Nwanganga Ihuoma Ubosi

All the Authors proof-read and approved the final manuscript for publication

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REFERENCES

Alaike,T, (2001). Role of free radicals in viral pathogenesis and mutation. *Reviews in Medical Virology*, *11*:87-101

Ana,L., Flores., Jennifer, N., Michael, C. & Scott, J.(2015). Urinary Tract Infections: Epidemiology, mechanism of infections and treatment options. *Nature Reviews Microbiology, 13(15):*269-284

Asadi, K.M.R., Habibi, M. & Bouzari, S. (2019). Urinary Tract Infection: Pathogenicity, antibiotic resistance and development of effective vaccines against uropathogenic *Escherichia coli*. *Molecular Immunology. 108*:56-67

Bakar,J.H., Qiu, J., Grine, K.(2018). Role of complementary and alternative therapies in infectious disease. *Prim.Care Clin Off Pract, 45*:533-539.

Bazzaz, B.S.F., Fakori, M., Khameneh, B. & Hosseinzadeh, H. (2019). Effects of omeprazole and caffeine alone and in combination with gentamicin and ciprofloxacin against antibiotic resistant Staphylococcus aureus and Escherichia coli strains. *Journal of Pharmacopuncture*, 22:49-54

Beerepoot, M.& Geerlings, S. (2016). Non-antibiotic prophylaxis for urinary tract infections. *Pathogens, 5*:36. Doi:10.3390/pathogens5020036.

Bibi, S.F.B., Sareh, D.F., Reza, A& Bahman, K. (2021). Deep insights into urinary tract infections and effective natural remedies. *African Journal of Urology, 27(6):*

Biswas, S., Thomas, N., Mandal, N., Mullick, A., Chandra, D., Mukherjee, S. (2013). *In-vitro* analysis of antibacterial activity of Vitamin C alone and in combination with antibiotics on Gram positive rod isolated from soil of a dumping site Kolkata. *International Journal of Pharmacy and Biological Sciences. 3*:101-110

Carlsson, S., Wiklund, N.P., Engstrand, L., Weitzberg, E., Lundberg, J.O. (2001). Effects of pH, nitrite, and ascorbic acid on nonenzymatic nitric oxide generation and bacterial growth in urine. *Nitric Oxide: Biology and Chemistry,* 5(6): 580-586. https//doi.org/10.1006/niox.2001.0371

Carpenter, K.J. (1986). *The history of Scurvy and Vitamin C*. Cambridge University Press; Cambridge, UK.

El-Gebaly, E., Essam, T., Hashem, S., El-Baky, R. (2013). Effect of levofloxacin and Vitamin C on bacterial adherence and performed biofilm on uretheral catheter surfaces *Journal* of *Microbial & Biochemical Technology, 4*:131-6.

Fazly, B.B.S., Sarabani, S., Khameneh, B., Hosseinzadeh, H. (2016). Effect of catechins, green tea extract and methylxanthines in combination with gentamicin against *Staphylococcus aureus* and *Pseudomonas aeruginosa*: combination therapy against resistant bacteria. *Journal of Pharmacopuncture,* 19:312-318.

Fazly, B.B.S., Sarabandi, S., Khameneh, B., Zahedian, O.S.M.R., Hosseinzadeh, H. (2018). In vitro evaluation of antibacterial activity of verbascoside, lemon verbena extract and caffeine in combination with gentamicin against drug-resistant *Staphylococcus aureus* and *Escherichia coli* clinical isolates. *Avicenna Journal of Phytomedicine, 8*:246-253.

Ge, M., O'Relly, A., Bullie, N., Twentyman, G., Sturt, J., Fitzpatrick, M. (2008). Vitamin C: Evidence, application and commentary. *NZ Fam Physician, 35*: 312-8

Habash, M.B., Van der, M.H.C., Busscher, H.J., Reid, G. (1999). The effect of water, ascorbic acid and cranberry derived supplementation on human urine and uropathogen adhesion to silicone rubber. *Canadian Journal of. Microbiology 45*:691-694. Doi: 10.1139/w99-065.

Hermila, H. (2017). Vitamin C and infections. *Nutrients. 9*:339

Humen, R & Weyers, E. (1973). Changes in leucocyte ascorbic acid during the common cold.

*Scottish Medical Journal,*18: 3-7.

Kasper, D.L., Fauci, A.S., Hauser, S.L., Longo, D.L., Jameson, J.L., Loscalzo, J. (2018). Urinary tract infections, pyelonephritis and prostatitis. In: *Harrison's Principles of Internal Medicine*, 20th edn. McGraw-Hill Education, New York.

Khameneh, B., Diab, R., Ghazvini, K., Fazly, B.B.S. (2016). Breakthroughs in bacterial resistance mechanisms and the potential ways to combat them. *Microbial Pathogenesis*, *95*:32-42

Khameneh, B., Iranshahy, M., Vahdati-Mashhadian, N., Sahebkar, A., Fazly, B.B.S.(2019). Non-antibiotic adjunctive therapy: a promising approach to fight tuberculosis. *Pharmacological Research, 146*: 104289.

Khameneh, B., Iranshahy, M., Soheili, V., Fazly, B.B.S. (2019). Review on plant antimicrobials: a mechanistic viewpoint. *Antimicrobial Resistance & Infection Control, 8*: 118

Martha, M & Edgar, C. (2019). An introduction to the epidemiology and burden of urinary tract infections *Therapeutic Advances in Urology* 11:1756287219832172. doi:10.1177/1756287219832172.

Mina, B., Simin, D., Azam, A., Neda, N & Seyed, M.G. (2020). High-dose intravenous Vitamin C reduces urinary tract infection post-kidney transplantation *African Journal of Urology, 26(37):*

Naing, L., Win, T., and Rusli, B. N. (2006). Practical Issues in Calculating the Sample Size.

Archives of orofacial sciences, 1:9-14.

Naidu, K.A. (2003). Vitamin C in human health and disease is still a mistery? An overview.
Nutrition Journal, 2:7
Novak, J & Fratamico, P. (2004). Evaluation of Ascorbic acid as a quorum sensing analogue to
control growth, sporulation and enterotoxin production in Clostridium perfringens
Journal of Food Science ,69: FMS72-8.
Ochoa-Brust, G.J., Fernandez, A.R., Villanueva-Ruiz, G.J., Velasco, R., Trujillo-Hernandez, B.,
Vasquez, C. (2007). Daily intake of 100mg ascorbic acid as urinary tract infection prophylactic agent during pregnancy. *Acta Obstetricia et Gynecologica Scandinavica*, *86*:783-787.
Okoroiwu, G.I.A. (2008). Comparative studies of urinary tract infection and reproductive tract
infection in Niger Delta States. Ph.D Thesis. Rivers State University of Science and Technology, Portharcourt, Nigeria.
Okoroiwu, G.I.A. (2018). Studies on the role of Escherichia coli in pregnancy related miscarriages (spontaneous abortion) in upland area of Rivers State of Nigeria. *FUW Trends in Science &Technology Journal, 3(2A):* 377-380.
Oudemans-van, S.H.M., Spoclstra-de, M.A.M., de-Ward, M.C. (2014). Vitamin C revisited *Critical Care, 18:*460
Peterlians, E. (1997). Oxidants and antioxidants in viral diseases. *Journal of Nutrition, 127*: 962S-965S.
Reedy, R. (2002). Urinary tract infections. Children's health.
Segal, A.W. (2005). How neutrophils kill microbes. *Annual Review of Immunology 23*:197-223.
Sheerin, N.S. (2011). Urinary tract infection. *Medicine, 39*: 384-389.
Sheerin, N,S & Glover, E.K. (2019). Urinary tract infection. *Medicine, 47*: 546-550
Storm, O., Tiran, S.J., Garcia-Mora, A., Dehesa-Davila, M & Naber, K.G. (2019). Risk factors
and predisposing conditions for urinary tract infection. *Therapeutic Advances in Urology, 11*: 1756287218814382
Svirbely, J.L & Szent-Gyorgyi, A. (1973). The chemical nature of Vitamin C. *Biochemical Journal, 26*: 865-70.
Verghese,R.J., Stephen,K.M & Alice, D. (2017). Antimicrobial activity of Vitamin C demonstrated on uropathogenic Escherichia coli and Klebsiella pneumonia. *Journal of Current Research in Scientific Medicine, 3(2*): 88.