EVALUATION OF ANTIMICROBIAL EFFECTS OF *NIGELLA SATIVA* AND *CAPSICUM FRUTESCENS* L.

By

Sonia Abid Bhatti

NUST2019MSCEE318862

A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

In

Environmental Engineering

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It is certified that the contents and forms of the thesis entitled

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Has been found satisfactory for the requirements of the degree of

Master of Science in Environmental Engineering

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I dedicate this thesis to my *Mother* and my Sister *Anam* who have been very supportive in all this master's journey

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Sonia Abid Bhatti

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ABREVIATIONS

FTIR	Fourier-transform infrared spectroscopy
GC-MS	Gas chromatography–mass spectrometry
N. sativa	*Nigella sativa*
DDD	Defined daily doses
WHO	World health organization
TQ	Thymoquinone

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ABSTRACT

Global burden of infectious diseases is on rise and there is a need to overwhelm them via environment friendly solutions. Number of antibiotics and vaccines are made by the scientist to protect human population. These antibiotics and vaccines have number of positive effects but unfortunately, they also cause number of long-term negative effects to human race by making the bacteria antibiotic-resistant, which is much harder to treat than those caused by non-resistant bacteria. Nature also plays its role by providing resources that may fight against disease-causing bacterial species. Plethora of plants have antimicrobial effects that can fight against various disease-causing microbes like; bacteria, viruses, and various fungi species. These microbes cause Methicillin-Resistant Staphylococcus Aureus, Diarrhea, Pneumonia and various human infections. Nature blessed antimicrobial materials have Thymoquinone, P-cymene, Pinene, Alkaloid, Limonene, Camphene and Melanin that disrupt cell membrane of microbes, inhibit cellular division and inhibit the formation of biofilm in bacterial species thus reducing the number of microbes. Nature blessed antimicrobials are not only available at a very low cost but also do not require any laborious techniques for their preparation against disease-causing microbes. In Pakistan 75 and 82.35% of married women are infected due to *Pseudomonas aeruginosa* and *Klebsiella species* respectively. This study augmented the effectiveness of *Nigella sativa* and *Capsicum frutescens* L. against *Pseudomonas aeruginosa* and *Klebsiella specie* by agar disc diffusion method. For the *Pseudomonas aeruginosa* observed zone of inhibition was 30mm and 25mm by 5g/20ml *Capsicum frutescens* L. and *Nigella sativa*, respectively for 10µL dilution. For *Klebsiella specie* no zone of inhibition was observed by *Capsicum frutescens L.* while 1mm zone of inhibition was observed by 7g/20ml *Nigella sativa* for 20µL dilution. Positive results of *Nigella sativa* and *Capsicum frutescens* L. were evaluated against both bacterial species streaked on single agar plate and by *Nigella sativa* 20mm zone of inhibition was observed while no zone of inhibition was observed by *Capsicum frutescens* L. FTIR analysis showed the presence of antimicrobial compounds in *Nigella sativa* and *Capsicum Frutescens* L. The obtained results indicated that *Nigella sativa* is effective against combine bacterial species. Thus, *N. sativa* may be used as an effective antimicrobial agent against selected bacterial infections.

Keywords: *Nigella sativa*, *Capsicum frutescens L.*, *Pseudomonas aeruginosa*, *Klebsiella species*, Antimicrobial activity, Disc diffusion method, FTIR, Meta-analysis.

INTRODUCTION

1.1 BACKGROUND

Infectious diseases constitute a public health concern for the whole world. All human problems like nail infection, diarrhea, abdominal cramps, bloody urine, loss of appetite, hair whitening, mouth infection, ear pain and skin infection are due to microbes. There is a global pandemic of resistant microbes that requires anti-microbial agents to fight with them. Anti-microbial agents basically disrupt the cellular structure of microbes thus inhibit the occurrence of various infectious diseases (Peterson, 2008). According to WHO the overall consumption of anti-microbial agents are between 4.4 to 64.4 Defined Daily Doses (DDD) per 1000 persons per day (Organization, 2018). Table below shows the antimicrobial consumption in some countries (Organization, 2018).

Table 1-1: National estimates of antimicrobial consumption in some countries

Country or area	Year	DDD	DDD/1000 inhabitants/day	Metric tones
African region				
Burkina Faso	2015	91 114 955	13.78	136.4
Burundi	2015	16 533 614	4.44	56.39
United Republic of Tanzania	2016	553 622 340	27.29	712.46
Region of the Americas				
Brazil	2016	1 724 124 919	22.75	2225.47
Canada	2015	223 101 184	17.05	242.69
Peru	2016	71 432 278	10.26	94.63
European Region				
Albania	2015	17 251 602	16.41	18.17
Armenia	2015	10 981 069	10.31	14.39
Austria	2015	38 081 745	12.17	38.84
Azerbaijan	2015	26 995 944	7.66	36.45
Belarus	2015	60 556 399	17.48	68.88
Belgium	2015	104 860 173	25.57	112.95

Bosnia and Herzegovina	2015	23 033 283	17.85	28.66
Bulgaria	2015	53 233 312	20.25	52.18
Croatia	2015	31 280 578	20.28	35.27
Cyprus	2015	8 389 248	27.14	8.10
Denmark	2015	36 848 791	17.84	53.25
Finland	2015	36 983 121	18.52	47.21
France	2015	628 986 424	25.92	764.02
Georgia	2015	33 152 652	24.44	33.04
Germany	2015	340 449 193	11.49	290.85
Greece	2015	134 139 320	33.85	139.18
Hungary	2015	58 664 563	16.31	57.27
Iceland	2015	2 146 458	17.87	2.18
Ireland	2015	39 318 933	23.27	50.22
Italy	2015	590 686 917	26.62	662.47
Kazakhstan	2015	114 558 903	17.89	162.22
Malta	2015	3 428 658	21.88	3.55
Netherlands	2015	60 338 150	9.78	55.66
Norway	2015	31 998 795	16.97	46.35
Poland	2015	337 067 701	24.3	306.61
Portugal	2015	67 089 554	17.72	79.84
Romania	2015	206 717 694	28.5	253.28
Russian Federation	2015	779 270 524	14.82	915.65
Serbia	2015	81 762 868	31.57	98.34
Slovakia	2015	48 154 016	24.34	49.55
Slovenia	2015	10 152 289	13.48	14.07
Spain	2015	304 475 774	17.96	343.91
Sweden	2015	48 834 144	13.73	72.70
Tajikistan	2015	68 493 070	21.95	121.12
Turkey	2015	1 090 722 974	38.18	1195.69

United Kingdom	2015	484 761 369	20.47	535.37
Uzbekistan	2015	97 762 994	8.56	185.90
Eastern Mediterranean Region				
Iran	2015	1 123 329 829	38.78	1178.61
Jordan	2015	29 836 359	8.92	21.23
Sudan	2015	497 782 564	35.29	675.75
Western Pacific Region				
Brunei Darussalam	2015	901 761	5.92	1.13
Japan	2015	658 400 748	14.19	524.9
Mongolia	2015	69 986 355	64.41	133.24
New Zealand	2015	38 036 523	22.68	36.85
Philippines	2015	304 852 740	8.21	260.55
Republic of Korea	2015	515 342 775	27.68	546.37

Many antibiotics impose various side effects and also some pathogens are resistant to various antibiotics so there is need to use herbal products in order to make antimicrobial agents (Namita & Mukesh, 2012).

1.2 PRESENT STUDY

In developing countries like Pakistan major public health issue is due to the poor environmental health and according to WHO residents of these low-income countries are more likely to die of communicable diseases like Malaria, Tuberculosis, Diarrhea and HIV/AIDS etc. Suitable preventive measures against these infectious and parasitic diseases should be adopted immediately. The preventive measures include cleaning practices and using antimicrobial agents that can fight against infectious and parasitic diseases. Antimicrobial agents can be extracted from plants that are available abundantly in the world. Plants like *Nigella sativa* and *Capsicum frutescens L.* are present abundantly in every region of the world with low cost. In Pakistan total area of 2.31 tons/ha is used for the production of *Capsicum frutescens L* (Khan et al., 2017) while *Nigella sativa* grows during the month of October and November in Pakistan with a yield of about 235 to 370 kg/acre (Rabbani et al., 2011). *Nigella sativa* and *Capsicum frutescens L*. are not only available easily in every part of the world but also have antimicrobial effects that can be used

against various disease-causing microbes like *Pseudomonas aeruginosa* and *Klebsiella species* (Dhanasekaran, 2019; Sarwar et al., 2020).

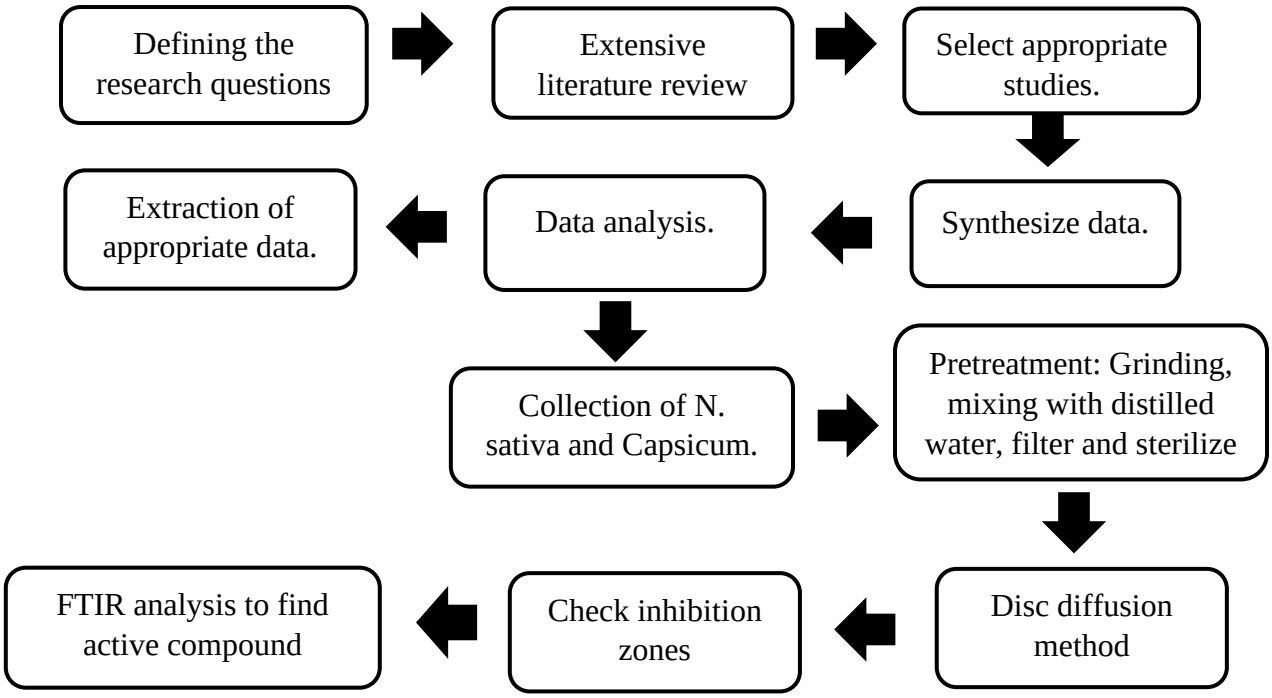


Figure 1-1: Experimental design of present study

1.3 SIGNIFICANCE AND NOVELTY

Infectious diseases are spreading rapidly in the whole world; it is an urgent need to know the antimicrobial effects of easily available materials. This study includes a comprehensive data on the antimicrobial effects of easily available materials and the outcome of this research will be beneficial for human population.

Previous research studies were mostly conducted on different plant extracts. Further the effects of plant extracts were evaluated on single bacterial colonies. Whereas, in present research solely the plants were crushed, mixed in distilled water filtered by Whatman filter paper no 1 and then this solution was used to evaluate its effect on combined bacterial colonies of *Pseudomonas aeruginosa* and *Klebsiella* specie.

1.4 STATEMENT OF THE PROBLEM

Presently the major cause of restlessness in the whole world is the spreading of infectious diseases. The number of confirmed deaths due to infectious diseases are growing day by day. As per current scenario human population have to visit many microbial contaminated sites like hospitals etc. and this increase the chances of getting infected by microbes. So, there is a need to keep safe human beings by using easily available materials that have anti-microbial effects.

1.5 OBJECTIVES

This study aimed to achieve two main objectives as follows:

(1) To conduct the meta-analysis for comprehensive study.

(2) To evaluate the anti-microbial effects of *Nigella Sativa* and *Capsicum Frutescens* L.

LITERATURE REVIEW

2.1 HERBS WITH ANTIMICROBIAL PROPERTIES

Herbal materials are used as an anti-microbial agent since ancient times. According to WHO 80% of the available drugs in the world are made up of herbal materials (Kirbağ et al., 2009). Plants are enriched with tannins, terpenoids, alkaloids and flavonoids (Cowan, 1999) that can act as anti-microbial agents as shown in table below;

Table 2-1 List of herbal materials for making anti-microbial agents

Sr. No	Herbal material	Constituent that cause anti-microbial effect	References
1.	Aloe	Complex mixture	(Martinez et al., 1996)
2.	Apple	Flavonoid derivative	(Hunter & Hull, 1993)
3.	Ashwagandha	Lactone	(Cowan, 1999)
4.	Bael tree	Terpenoid	(Rana et al., 1997)
5.	Barberry	Alkaloid	(McDevitt et al., 1996; Omulokoli et al., 1997)
6.	Basil	Terpenoids	(Wan et al., 1998)
7.	Bay	Terpenoids	(Cowan, 1999)
8.	Betel pepper	Essential oils	
9.	Black pepper	Alkaloid	(Ghoshal et al., 1996)
10.	Blueberry	Monosaccharide	(Ofek et al., 1996)
11.	Brazilian pepper tree	Terpenoids	(Cowan, 1999)
12.	Buchu	Terpenoid	
13.	Burdock	Polyacetylene, tannins, terpenoids	
14.	Buttercup	Lactone	
15.	Caraway	Coumarins	(Bose, 1958; Elsevier, 1978; Hamburger & Hostettmann, 1991; Scheel, 2016)

Sr. No	Herbal material	Constituent that cause anti-microbial effect	References
16.	Cascara sagrada	Polyphenols, Anthraquinone	(Cowan, 1999)
17.	Cashew	Polyphenols	
18.	Ceylon cinnamon	Terpenoids, tannins	
19.	Chamomile	Phenolic acid, Coumarins	(Bose, 1958)
20.	Chapparal	Lignan	(Cowan, 1999)
21.	Chili peppers, paprika	Terpenoid	
22.	Clove	Terpenoid	(Cowan, 1999)
23.	Coca	Alkaloid	
24.	Cranberry	Monosaccharide	(Bose, 1958; Ofek et al., 1996; Ofek et al., 1991)
25.	Dill	Terpenoid	(Cowan, 1999)
26.	Eucalyptus	Polyphenol, Terpenoid	
27.	Fava bean	Thionin	
28.	Gamboge	Resin	
29.	Garlic	Sulfoxide, Sulfated terpenoids	(Naganawa et al., 1996; San-Blas et al., 1993; San-Blas et al., 1989; Yoshida et al., 1987)
30.	Apple pomace	Proanthocyanidins, flavonoids	(Lu & Foo, 2000; Schieber et al., 2000; Sudha et al., 2007)
31.	Banana leaves	Polyphenols (terpenoid and flavonoids)	(Marie-Magdeleine et al., 2010)
32.	Banana	Catechin and gallocatechin	(Babbar et al., 2011)
33.	Beet root pomace	Betalains and 1,1-Diphenyl-2-picryl-hydrazyl (DPPH)	(Čanadanović-Brunet et al., 2011)

Sr. No	Herbal material	Constituent that cause anti-microbial effect	References
34.	Black currant pomace	Anthocyanins, linolenic acid and other fatty acids	(Holtung et al., 2011)
35.	Broccoli by-products	Glucosinolates, phenolic acids, flavonoids and vitamin C	(Dominguez-Perles et al., 2011; Domínguez-Perles et al., 2010)
36.	Cabbage, watermelon rind and peach peels	As a carbon source for synthesis of carotenoids using Blakeslea trispora	(Papaioannou & Liakopoulou-Kyriakides, 2012)
37.	Cashew apple waste	Vitamin C, organic acids, antioxidants, unsaturated fatty acids, minerals	(Sancho et al., 2015; Sivagurunathan et al., 2010)
38.	Cauliflower cull	Curcumin and phenethyl isothiocyanate	(Wadhwa et al., 2015)
39.	Citrus juice, pulp and seed	Limonoids-highly oxygenated triterpenoid	(Rudra et al., 2015)
40.	Grape and pomegranates peels	Flavonoids phenolic acids	(Babbar et al., 2011; Jayaprakasha et al., 2001; Li et al., 2006; Shrikhande, 2000)
41.	Gooseberry peels	Polyphenolic compounds e.g. ellagic and gallic acids and corilagin	(Chitturi et al., 2013; Poltanov et al., 2009)
42.	Guava peel and pulp	Polyphenolic compounds, melanin, dietary fibre	(Chitturi et al., 2013; Jiménez-Escrig et al., 2001)
43.	Litchi pericarp	Phenolics (epicatechin, procyanidins, cyanidin-3-glucoside, and quercetin-3-rutinoside), flavonoids and anthocyanin (cyanidin3-rutinoside)	(Duan et al., 2007; Jiang et al., 2013; Li et al., 2012; Sarni-Manchado et al., 2000; Zhang et al., 2004)

Sr. No	Herbal material	Constituent that cause anti-microbial effect	References
44.	Litchi seed	Proanthocyanidins, flavonoids, steroids, and sesquiterpenes	(Prasad et al., 2009; Singh et al., 2013; Xu et al., 2011)
45.	Litchi bark	Flavonoids, polyphenols, anthocyanins and vitamin C	(Queiroz et al., 2012; Queiroz et al., 2015)
46.	Longan seeds	polyphenolic compounds	(Panyathep et al., 2013)
47.	Mango peel	Syringic acid, quercitin, mangiferin pentoside and ellagic acid,carotenoids, vitamins, enzymes and dietary fibres	(Ajila et al., 2007; Ajila et al., 2010; Berardini et al., 2005; Larrauri et al., 1997; Schieber et al., 2000)
48.	Mango seed kernels	Gallic acid	(Al-Farsi & Lee, 2008; Puravankara et al., 2000)
49.	Mango pulp and ripe peel	Carotenoids (b-carotene)	(Chen et al., 2004; Varakumar et al., 2011)
50.	Onion waste	Quercetin	(Hertog et al., 1992; Kim & Kim, 2006; Ly et al., 2005; Nuutila et al., 2003)
51.	Rambutan peels	Ellagic acid, corilagin and geraniin	(Palanisamy et al., 2008; Thitilertdecha et al., 2010)
52.	Tomato pomace	Sterols, tocopherols, carotenes (Lycopene), terpenes, flavonoids and ascorbic acid	(Kalogeropoulos et al., 2012)
53.	Ginseng	Saponins	(Cowan, 1999)
54.	Glory lily	Alkaloid	
55.	Goldenseal	Alkaloids	(Freiburghaus et al., 1996; Omulokoli et al., 1997)
56.	Gotu kola	Terpenoid	(Cowan, 1999)
57.	Grapefruit peel	Terpenoid	(Stange Jr et al., 1993)
58.	Green tea	Flavonoid	(Cowan, 1999)

Sr. No	Herbal material	Constituent that cause anti-microbial effect	References
59.	Hemp	Organic acid	
60.	Henna	Phenolic	
61.	Hops	Phenolic acid, terpenoids	
62.	Horseradish	Terpenoids	
63.	Hyssop	Terpenoids	
64.	(Japanese) herb	Terpene	(Kadota et al., 1997)
65.	Legume (West Africa)	Flavone	(Perrett et al., 1995)
66.	Lemon balm	Polyphenols	(Warren, 1995)
67.	Lemon verbena	Terpenoid	(Cowan, 1999)
68.	Licorice	Phenolic alcohol	
69.	Mountain tobacco	Lactones	
70.	Oak	Polyphenols, Flavonoid	(Pelkonen et al., 1997)
71.	Olive oil	Aldehyde	(Kubo et al., 1995)
72.	Onion	Sulfoxide	(Vohora et al., 1973)
73.	Orange peel	Terpenoid	(Stange Jr et al., 1993)
74.	Oregon grape	Alkaloid	(Freiburghaus et al., 1996; Omulokoli et al., 1997)
75.	Pao d'arco	Terpenoids	(Cowan, 1999)
76.	Papaya	Mix of terpenoids, organic acids, alkaloids	(Burdick, 1971; Osato et al., 1993; Satrija et al., 1995)
77.	Pasque-flower	Lactone	(Cowan, 1999)
78.	Peppermint	Terpenoid	
79.	Periwinkle	Alkaloid	
80.	Peyote	Alkaloid	
81.	Poppy	Alkaloids and others	

Sr. No	Herbal material	Constituent that cause anti-microbial effect	References
82.	Purple prairie clover	Flavonol	(Hufford et al., 1993)
83.	Quinine	Alkaloid	(Cowan, 1999)
84.	Rauvolfia, chandra	Alkaloid	
85.	Rosemary	Terpenoid	
86.	Sainfoin	Polyphenols	(Ali-Shtayeh et al., 1997; Jones et al., 1994)
87.	Savory	Terpenoid	
88.	Senna	Anthraquinone	(Cowan, 1999)
89.	St. John's wort	Anthraquinone	
90.	Tansy	Terpenoid	
91.	Tarragon	Terpenoid, Polyphenols	
92.	Thyme	Terpenoid, Phenolic alcohol, Polyphenols, Flavones	
93.	Tree bard	Flavonol, Lactone	(Kubo et al., 1992, 1993; Kubo et al., 1994)
94.	Turmeric	Terpenoids	(Apisariyakul et al., 1995)
95.	Valerian	Terpenoids	(Cowan, 1999)
96.	Willow	Phenolic glucoside, Polyphenols, Terpenoid	
97.	Wintergreen	Polyphenols	
98.	Woodruff	Coumarin	(Hamburger & Hostettmann, 1991; Scheel, 2016)

2.2 DISEASE CAUSING MICROBES

Various infectious diseases are spreading nowadays due to different microbes like; Gram-positive bacteria, Gram- negative bacteria, *Candida albicans*, *Staph. Aureus*, *Esch. Coli*, Gram-positive

cocci, *Microsporum canis*, *Trichophyton mentagrophytes*, *Trichophyton interdigitale*, Four species of *Trichophyton rubrum*, *Staphylococcus epidermidis*, *Micrococcus luteus*, *Listeria monocytogene*, *Bacillus cereus*, *Pseudo. aeruginosa*, *Salmonella enteritidis*, *Sal. Typhimurium* and *Shigella flexneri*.

Table 2-2: Infectious diseases cause by microbes

Infectious disease	Microbe that causes the disease	Type of microbe	References
methicillin-resistant *Staphylococcus Aureus* (MRSA).	Gram-positive bacteria	Bacteria	(Doernberg et al., 2017)
Pneumonia, bloodstream infections, wound or surgical site infections.	Gram- negative bacteria	Bacteria	(Control & Prevention, 2011)
Growth of *Candida* in the bloodstream or internal organs like the kidney, heart, or brain cause infections in these body parts.	*Candida albicans*	Fungus	(Akpan & Morgan, 2002)
Bloodstream infections, pneumonia, or bone, tissue infections i.e boils and joint infections.	*Staph. aureus*	Bacteria	(Lowy, 1998)
Urinary tract infection, traveler's diarrhea, and pneumonia.	*Esch. coli*	Bacteria	(Makvana & Krilov, 2015)
Immunologic infections	Gram-positive *cocci*	Bacteria	(Gregersen, 1978)
Tinea corporis (B35. 6)	*Microsporum canis*	Fungus	(Kokollari et al., 2015)
Ringworm in mice.	*Trichophyton mentagrophytes*	Fungus	(Williford & Wagner, 1982)
Dermatophytosis	*Trichophyton interdigitale*	Fungus	(Zhang et al., 2019)

Infectious disease	Microbe that causes the disease	Type of microbe	References
Nosocomial infections	*Staphylococcus epidermidis*	Bacteria	(Otto, 2009)
Foodborne bacterial illness causes to unborn babies, newborns and people with weakened immune systems	*Listeria monocytogene*	Bacteria	(Edelson & Unanue, 2000)
Diarrheal and toxico-infections	*Bacillus cereus*	Bacteria	(Jessberger et al., 2020)
Acute gastroenteritis and human infections worldwide	*Vibrio paraheamolyticus* ATCC 17802	Bacteria	(Martinez-Urtaza et al., 2004)
Superficial and ear infections in humans	*Vibrio alginolyticus* ATCC 33787	Bacteria	(Reilly et al., 2011)
Human infections; burn, urinary tract and human airways infections.	*Pseudo. aeruginosa* ATCC 27853	Bacteria	(Cao et al., 2017)
Bacterial gastroenteritis	*Salmonella enteric serovar typhimurium* ATCC 14028	Bacteria	(Alexander et al., 2016)
Diarrhea, fever, and abdominal cramps	*Salmonella enteritidis*	Bacteria	(Rodrigue et al., 1990)
Gastroenteritis and focal infections	*Sal. typhimurium*	Bacteria	(Jung et al., 2020)
Diarrhea (sometimes bloody), fever, and stomach cramps.	*Shigella flexneri*	Bacteria	(Duncan-Lowey et al., 2020)

2.3 *NIGELLA SATIVA* PRODUCING COUNTRIES

Nigella sativa grows mostly in Southern Europe, North Africa, Southwest Asia, Middle Eastern Mediterranean region, India, Pakistan, Syria, Turkey and Saudi Arabia. In India *N.sativa* productivity is between 300-500 kg ha^{-1} (Mehmood et al., 2018).

2.3.1 Trends, area, production and yield of *Nigella sativa* in Pakistan

In Quetta and Kalat *Nigella sativa* yield range from 845 to 975 kg ha^{-1}. With improved technologies Nigella sativa can grow between a yield of 1500 to 1800 kg ha^{-1}(Zahoor & Abdul, 2007).

2.3.2 Growing areas of *Nigella sativa* in Pakistan

Major producing area of *N. sativa* are Kohat, Lahore, Faisalabad and Hatter with 82.3, 108.5, 109.7 and 108.9 g yield/row (Rabbani et al., 2011).

2.4 *CAPSICUM FRUTESCENS* L. PRODUCING COUNTRIES

In the whole world *Capsicum Frutescens* L. produce around 7 million tons on 1.5 million hectares land. In India production of Capsicum Frutescens L. production is 11 lakh tons, in Mexico 3 lakh tons and in Pakistan 2 lakh tons (Khokhar & NARC, 2013).

2.4.1 Trends, area, production and yield of *Capsicum frutescens* L. in Pakistan

In Pakistan since 2000-01 to 2009-10 production of *Capsicum Frutescens* L. range from 174.6 to 188.9 thousand tones. Sindh is the major pricing area with production of 122.9 thousand tons (Khokhar & NARC, 2013).

2.4.2 Growing areas of *Capsicum frutescens* L. in Pakistan

Punjab produces 6.3 %, Balochistan 33.4 %, KPK 0.6 % and Sindh produces 89.7 % *Capsicum Frutescens L.* In Punjab, Sindh, KPK and Baloshistan *Capsicum Frutescens* L. produce in Kasur, Okara, Pakpattan, Sahiwal, Multan, Sheikhapura, Khanewal, Vehari, Bahawal Nagar, Mirpurkhas, Hyderabad, Badin, Sanghar, Mohmand Agency, Bajour, Dir, Kohat, Killa Saifullah, Khuzdar, Loralai and Musa Khel (Khokhar & NARC, 2013).

2.5 *NIGELLA SATIVA* AND *CAPSICUM FRUTESCENS L.* AS AN ANTIMICROBIAL AGENT

Nigella sativa contains more than 100 valuable elements including proteins, vitamins and essential fatty acids that have antimicrobial effects. Due to the presence of thymoquinone and

thymohydroquinone in *N. sativa* it can fight against microbial infectious diseases (Bakal et al., 2017).

***Capsicum frutescens* L**. has medicinal importance in the whole world. It contains Capsaicinoids that have more than 20 alkaloids (Bakht et al., 2020). *Capsicum* has strong antimicrobial properties and thus it is good to use this in daily food items.

Table 2-3: *Nigella sativa* and *Capsicum frutescens L*. as an antimicrobial agent

Sr. No	Name of material	Constituent that causes antimicrobial effect	Adopted methodology	Findings	References
1.	***Nigella sativa***	Presence of Thymoquinone and Melanin	Paper disc diffusion method	Antibacterial effect against Staphylococcus.	(Bakathir & Abbas, 2011; Hassieb, 2006; Roy et al., 2006)
		Fixed oil and Thymoquinone of N. Sativa	-	Effective against many microbes Most effective against Aspergillus species.	(Agarwal et al., 1979; Ali & Blunden, 2003)
		Thymoquinone, p-cymene and pinene	Disc diffusion method	Thymoquinone is the main component that causes antimicrobial effects	(Roy et al., 2006)
		Essential oil of N. sativa	Plate diffusion method	Most effective against Bacillus subtilis	(El-Kamali et al., 1998)

Sr. No	Name of material	Constituent that causes antimicrobial effect	Adopted methodology	Findings	References
		Crude alkaloid and water extract of the seed	-	Gram negative was most effected than Gram positive	(Morsi, 2000)
2.	***Capsicum frutescens* L.**	Low pH of fruit	Disk diffusion method and Well diffusion method	Extracts of Capsicum fruits are suitable for antibacterial activities	(Careaga et al., 2003; Koffi-Nevry et al., 2012; Tano et al., 2008)
		Isopropanol extracts	Growth inhibition test	Cinnamic and M-coumaric acids from Chilli extracts are effective against bacterial species.	(Dorantes et al., 2000)
		Capsaicin-induced alterations in the pH	-	Prevent microbial infections	(Tellez et al., 1993)
		Presence of Capsaicin	Inhibit CT production	Effective against V. cholera	(Omolo et al., 2014)
		Presence of Capsaicin and Capsaicinoids	Disk diffusion method	Capsaicinoids is the main component that causes	(Das et al., 2018)

Sr. No	Name of material	Constituent that causes antimicrobial effect	Adopted methodology	Findings	References
				antibacterial effect.	

2.6 CHEMICAL COMPOSITION OF *NIGELLA SATIVA*

Nigella sativa contains valuable fixed oils, volatile oils, protein, carbohydrates and more than 100 valuable elements. According to science *N. sativa* contains proteins, vitamins and essential fatty acids that have antimicrobial effects. Due to the presence of thymoquinone and thymohydroquinone in *N. sativa* may fight against microbial infectious diseases (Bakal et al., 2017).

Table 2-4: Chemical composition of *Nigella sativa* (Devi et al.)

Constituents	Chemical constituents	Pharmacological Activity
Fixed Oils	Linoleic acid (Omega-6 and 3) and Oleic acid	Prevents infection and chronic ailments
Volatile Oil	Thymoquinone, Dithymoquinon, Thymohydroquinone, Thymol, nigellone	Antineolastic, Anti-oxidant, Anti-inflammatory effect both invite and in vivo. TQ effect on Apoptosis. TQ and Nigellone –Anti-spasmodic and bronch-dilator.
Protein	Arginine, Aspartic acid, leucine, Glycine, Valine, Histidine, Methionine, Phenylalanin	Hormonal regulation, Regulation of cell-division, Immune system actions
Carbohydrates	Glucose, Xylose, Arabinose,	Energy production & storage, Build macromolecules, sparing protein, Lipid

Constituents	Chemical constituents	Pharmacological Activity
		metabolism, Glucose stored as glycogen.
Minerals	Ca, K, Fe, Zn, Mg, phosphorus, Na, Mn, Cu, Selenium	Calcium utilizes Vitamin C, Zinc-Vitamin A, Magnesium-B, Selenium for Vitamin E absorption.
Saponins	α-Hederin (melanthin), Hederagenin (melanthigenin)	Alpha-hederin & Thymoquinone inhibit four tumor cell lines-A549, HEp-2, HT-29, MIA paca2-both apoptotic and necrosis.
Alkaloids	Nigelicine, Nigellimine, Nigellidine	Bitter in taste, strengthen tissue, and eliminate excess acids, helps in digestive problems.
Vitamins	Vitamin A and C, Thiamin, Riboflavin, Pyridoxine, Niacin, Folacin	Help in the utilization of energy nutrient, maintain normal body tissue, and act as a regulator.

2.6.1 GC-MS analysis of ethanolic extract of *Nigella sativa*

Ethanolic extracts of *Nigella sativa* was analyzed by GC-MS. Graph and table below shows the presence of various compound in *N. sativa* along with anti-microbial compound.

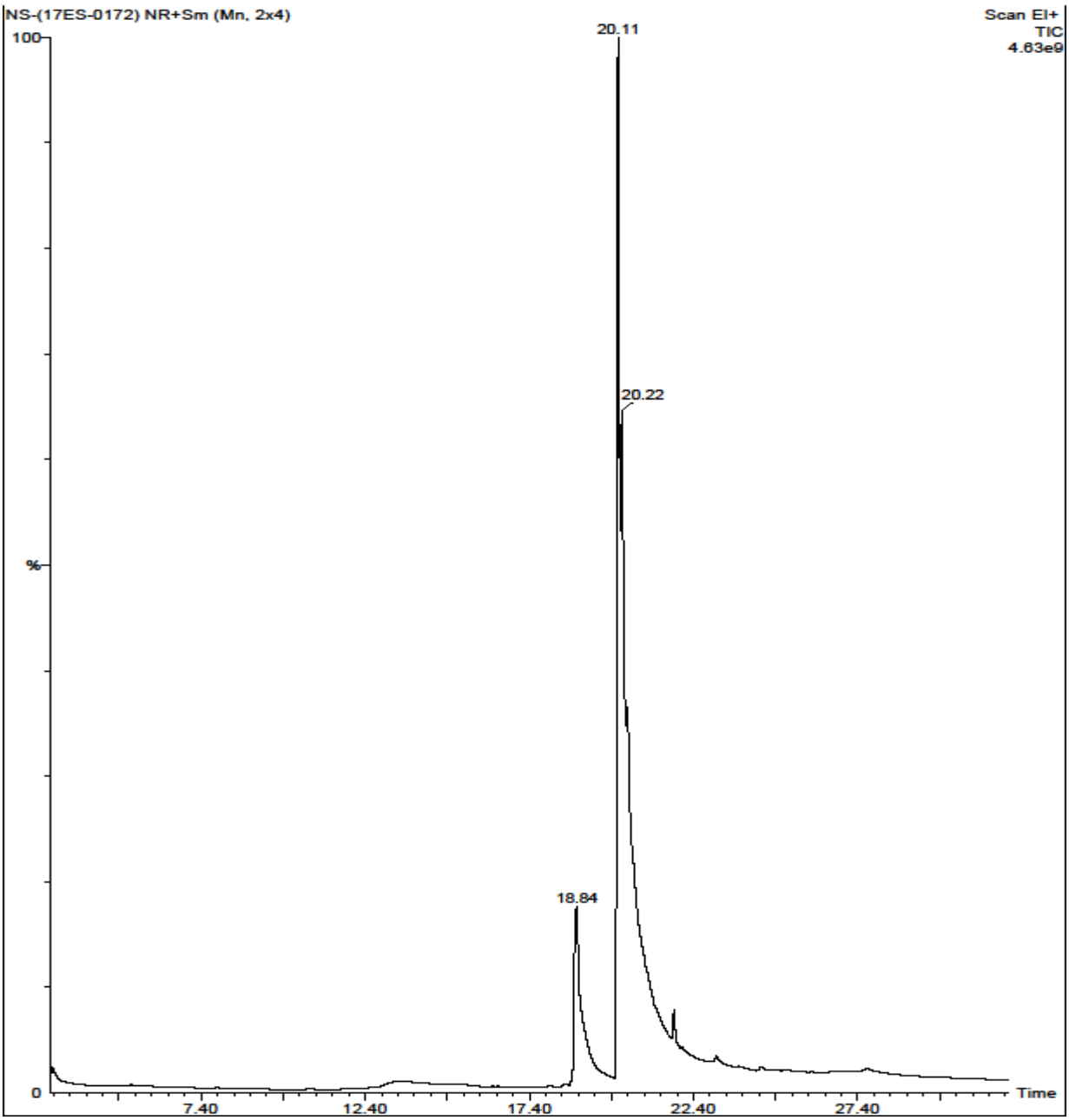


Figure 2-1: GC-MS analyses of ethanolic extract of *N. sativa* (Devi et al.)

Table 2-5: GC-MS analyses of ethanolic extract of *N. sativa* (Devi et al.)

S.No	Phytochemical compounds	Retention time	Molecular formula	Molecular weight	Pharmacological Activity
1.	Hexadeconoic acid, Ethyl Ester	3.192	$C_{18}H_{36}O_2$	284	Antioxidant, Flavor, Hepoc-cholestrolemic pesticide-5 Alpha reductase inhibitor
2.	Ecosonoic acid, Ethyl Ester	9.32	$C_{20}H_{40}O_2$	312	Lower lipid levels in adults

S.No	Phytochemical compounds	Retention time	Molecular formula	Molecular weight	Pharmocalogical Activity
3.	9,12 Decadecadienoyl, Chloride (Z,Z)	20.205	$C_{18}H_{31}OCl$	298	Cancer preventive, Anti-inflammatory, Hepato-protective, Insectifuge, Hypo-choletrolemic
4.	Z,E-2-Methyl-313, Octadecadien-I-OL	20.105	$C_{19}H_{36}O$	280	Anti-microbial activity and Anti-carcinogenic activity
5.	9,12 Octadecadienoic acid (Z,Z)	20.405	$C_{18}H_{32}O_2$	280	Anti-inflammatory,Nematicide and Insectifuge

2.7 CHEMICAL COMPOSITION OF *CAPSICUM FRUTESCENS L.*

Capsicum frutescens L. has medicinal importance in the whole world. It contains Capsaicinoids that have more than 20 alkaloids (Bakht et al., 2020). *Capsicum frutescens L.* has strong antimicrobial properties and thus it is good to use this in daily food items.

2.7.1 GC-MS analysis of n-hexane and chloroform extract of *Capsicum frutescens L.*

N-hexane extracts of *Capsicum frutescens L.* was analyzed by GC-MS. Graph and table below shows the presence of various compound in *Capsicum frutescens L.* along with anti-microbial compound.

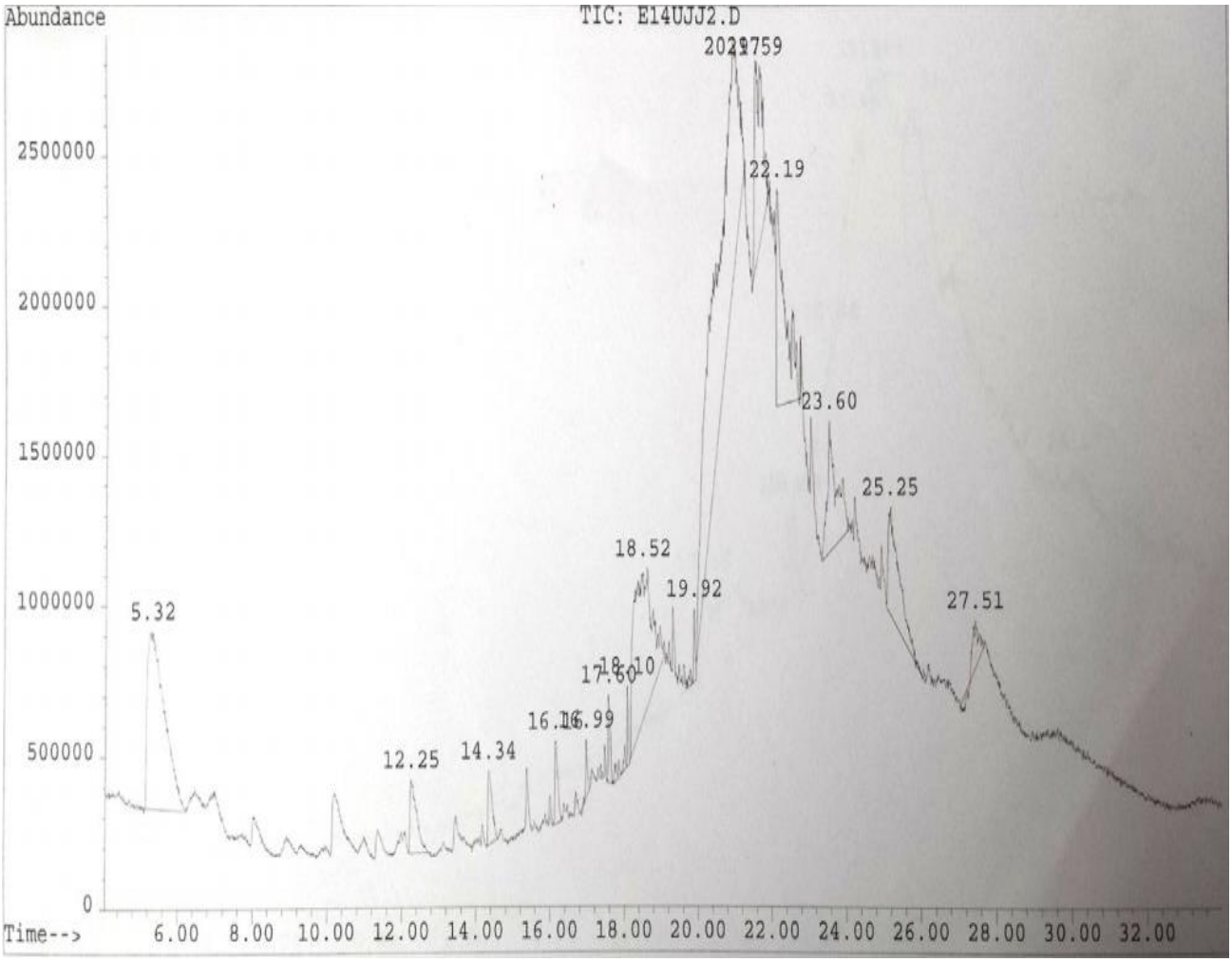


Figure 2-2: GC-MS analyses of n-hexane extract of *Capsicum frutescens L*. (Gurnani et al., 2016)

Table 2-6: Chemical composition of n-hexane extracts of *Capsicum frutescens L*. seeds analyzed by GC-MS (Gurnani et al., 2016)

S.No	Name of compounds	Retention time	Molecular weight	Molecular formula	Pharmocalogical Activity
1.	3-Carene	5.32	136	$C_{10}H_{16}$	Inhibit growth of Clostridium difficile, paraputrificum and perfringens, Staphylococcus aureus, Escherichia coli and Bacteroides fragilis (Koziol et al., 2014)
2.	Hexadecane	12.25	226	$C_{16}H_{34}$	Have antibacterial activity (Kumaresan et al., 2014)
3.	Octadecane	14.34	254	$C_{18}H_{38}$	Have antibacterial activity (Rouis-Soussi et al., 2014)

S.No	Name of compounds	Retention time	Molecular weight	Molecular formula	Pharmocalogical Activity
4.	Eicosane	16.16	282	$C_{20}H_{42}$	Have antimicrobial activity (Farzaei et al., 2014)
5.	10-Heneicosene	16.98	294	$C_{21}H_{42}$	No pharmocalogical activity.

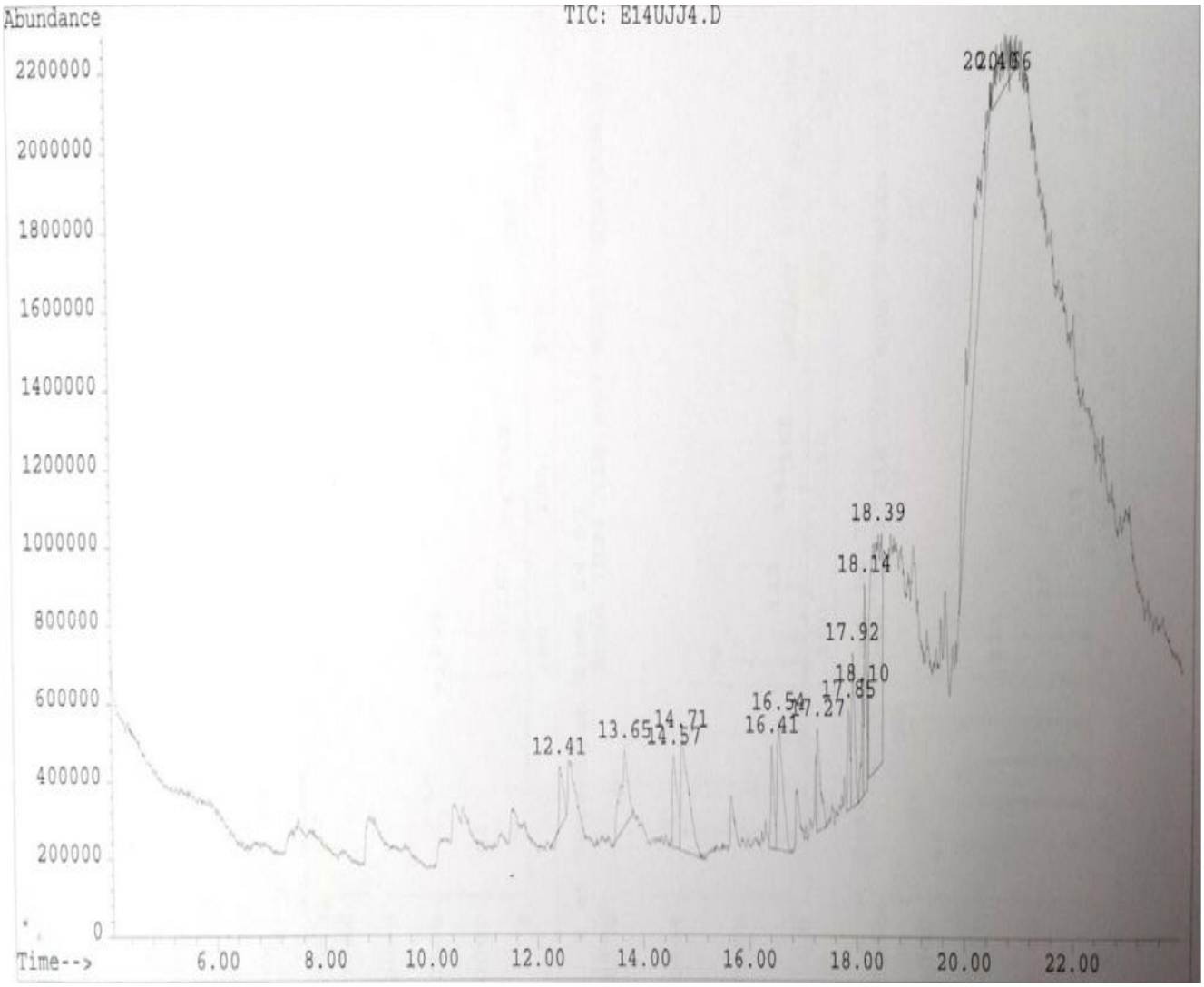


Figure 2-3: GC-MS chromatogram of the chloroform extract of the seeds of *Capsicum frutescens L*. (Gurnani et al., 2016)

Table 2-7: Chemical composition of chloroform extracts of *Capsicum frutescens L*. seeds analyzed by GC–MS (Gurnani et al., 2016)

S.No	Name of compounds	Retention time	Molecular weight	Molecular formula	Pharmocalogical Activity
1.	1-Phenyloctane	12.41	190	$C_{10}H_{16}$	No pharmocalogical activity.

S.No	Name of compounds	Retention time	Molecular weight	Molecular formula	Pharmocalogical Activity
2.	Phenol,2,4-bis(1,1-dimethyethyl)	13.65	206	$C_{16}H_{34}$	Effective against many microbes (Zhao et al., 2020)
3.	Octadecane	14.57	254	$C_{18}H_{38}$	Have antimicrobial activity (Rouis-Soussi et al., 2014)
4.	1-Hexadecene	14.71	224	$C_{20}H_{42}$	Have antimicrobial activity (Mou et al., 2013)
5.	Eicosane	16.41	282	$C_{21}H_{42}$	Anti-androgenic and aldose reductase inhibitor (Khatua et al., 2016)

Table 2-8: Chemical composition of market available antibiotics against *Pseudomonas aeruginosa* and *Klebsiella species*

Name of medicine	Chemical composition
Cephalosporin	Carbonyl group, Carboxylic acid, 6 membered dihydrothiazine ring, B lactam ring
Dihydrostreptomycin	Streptidine, hydroxyl alcoholic group, N-methyl-L-glucosamine unit
Moxifloxacin	1-Cyclopropyl-6-fluoro-7-((4aS,7aS)-hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid
Chloramphenicol	Nitrobenzene ring, an amide bond, alcoholic function
Ciprofloxacin	Naldixic acid, 1-cyclopropyl-6-fluoro-1, 4dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid hydrochloride

There are some compounds present in market available antibiotics similar to that present in *Nigella sativa* and *Capsicum frutescens L*. i.e. Carbonyl group, Carboxylic acid, hydroxyl alcoholic group, 8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, alcoholic and Naldixic acid.

2.8 ANTI-MICROBIAL COMPOUNDS

Thymoquinone, Melanin, P-cymene, Pinene, Alkaloid, Limonene and Camphene are the major anti-microbial compounds present in *N. sativa* and *Capsicum frutescens L*.

2.8.1 Thymoquinone

Thymoquinone is a compound that have remarkably antisepsis activity at specific dose (Alkharfy et al., 2018; Alkharfy et al., 2015; Alkharfy et al., 2011). Sepsis is such condition in which NO is released at faster rate, which causes systematic disfunction and tissue injuries in human and animals (Rabuel et al., 2010; Tsolaki et al., 2017). Thymoquinone modulates the production of NO thus saving humans and animals from multiple organ disfunction syndrome (Galley, 2011; Ichinose et al., 2007). Thymoquinone is the main component present in *Nigella Sativa* that was found to be effective against Avian influenza virus (Salem & Hossain, 2000; Umar et al., 2016). If the cells have consumed *Nigella sativa* then it decreases the replication of virus in that body (Ulasli et al., 2014) and according to another study after consuming *Nigella sativa* the virus survival becomes difficult in the cell (Ahmad et al., 2020).

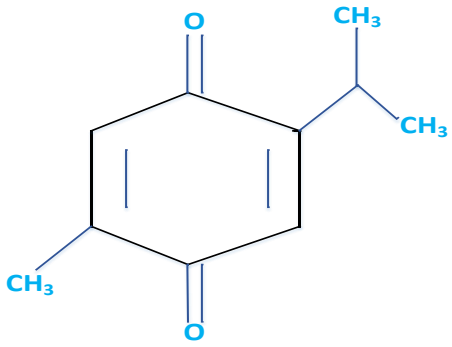


Figure 2-4: Chemical structure of Thymoquinone

2.8.2 Melanin

Melanin is an efficient green agent that has vast application in the field of biomedical. Melanin consumes antioxidant activity. (Da Silva et al., 2017; Ju et al., 2011; Rageh et al., 2015; Schweitzer et al., 2010; Silvestri et al., 2017) Antioxidants are basically that substances that protects our bodies from the free radicals, which may otherwise cause various diseases.

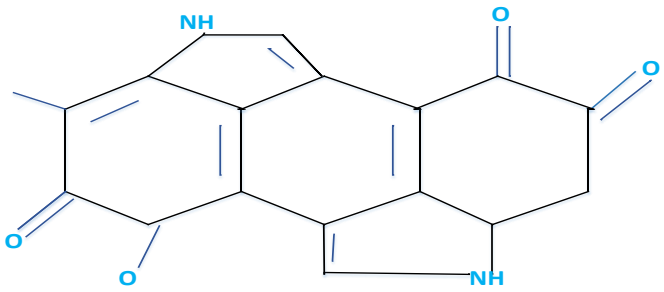


Figure 2-5: Chemical structure of Melanin

2.8.3 P-cymene

P-cymene is found in many plants (Benchaar et al., 2008; Singh et al., 1999). It is used as an important agent in many drugs (Selvaraj et al., 2002). It is widely present in orange juice, grape fruit, mandarin, carrots, raspberries, butter, nutmeg, oregano, and almost in every spice (Siani et al., 1999). P-cymene have anti-inflammatory (Bonjardim et al., 2012), analgesic (Quintans et al., 2013) and anti-tumor effects (Li et al., 2016). It also possesses antioxidant effects (Nickavar et al., 2014; Yvon et al., 2012).

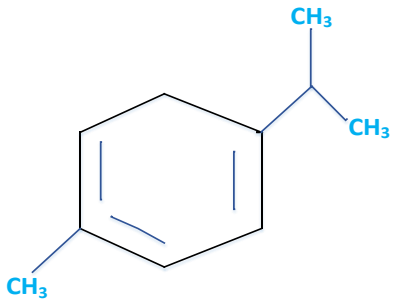


Figure 2-6: Chemical structure of P-cymene

2.8.4 Pinene

Pinene is the natural compound found in citrus fruits. Pinene has various potential benefits such as it has anti-inflammatory, anti-microbial, antioxidant and neuroprotective effects (Di Rauso Simeone et al., 2020).

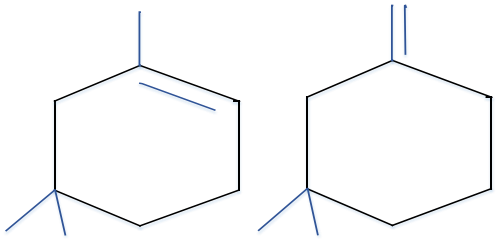


Figure 2-7: Chemical structure of a and b pinene

2.8.5 Alkaloid

Alkaloid is the natural compound found in many plants. Presence of alkaloids in plants protect them from destruction of various insects (Zhang et al., 2005).

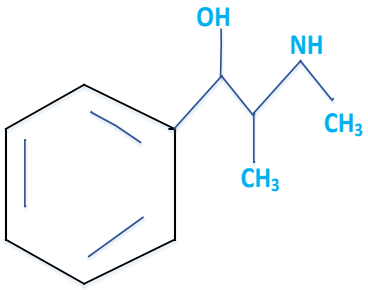


Figure 2-8: Chemical structure of Alkaloid

2.8.6 Limonene

Limonene is chemical found mostly in citrus fruits (Rodríguez et al., 2011). Limonene has several health benefits and belongs to the group of terpenes (Miguel, 2010). These chemicals have strong aromas which protect plants from predators. Limonene also have anti-inflammatory (Yoon et al., 2010) and antioxidant effects (Miguel, 2010).

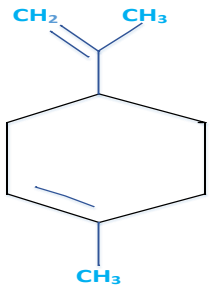


Figure 2-9: Chemical structure of Limonene

2.8.7 Camphene

Camphene is a monoterpene found in many plants (Russo & Marcu, 2017). Terpenes are those chemicals which have strong aromas which protect plants from predators (Miguel, 2010).

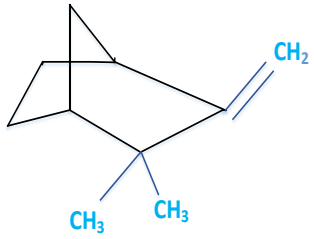


Figure 2-10: Chemical structure of Camphene

Table 2-9: Extracts of *Capsicum frutescens* L. and *Nigella Sativa* effective against microbes

Substrates	Effective against microbes	References
Extracts of *Capsicum frutescens* L.	*Bacillus cereus* and *subtilis*, *Clostridium sporogenes*, and *tetani*, *Streptococcus pyogenes*, *Vibrio cholerae*, *Staphylococcus aureus*, and *Salmonella typhimurium*	(De Lucca et al., 2006; Koffi-Nevry et al., 2012; Shariati et al., 2010)
Nigella sativa	Bacteria (gram-positive and gram-negative), *Candida albicans*, *Staph. Aureus*, *Esch. Coli*, Gram-positive *cocci*, *Microsporum canis*, *Trichophyton mentagrophytes*, *Trichophyton interdigitale*, Four species of *Trichophyton rubrum* , *Staphylococcus epidermidis* , *Micrococcus luteus*, *Listeria monocytogene*, *Bacillus cereus* , *Vibrio parahaemolyticus*, *Pseudo. aeruginosa* , *Salmonella enteritidis*, *Sal. Typhimurium* and *Shigella flexneri*	(Alshareef, 2019; Chaieb et al., 2011; Halawani, 2009; Hanafy & Hatem, 1991; Hannan et al., 2008; Hosseinzadeh et al., 2007; Khan et al., 2003)

2.9 ANTIMICROBIAL MECHANISM

Plants have plethora of constituents that impose antimicrobial effects (Casciaro et al., 2019; Dewapriya et al., 2018; Mickymaray et al., 2016). Basically, two major groups of antibiotics extracted from plants are; (1) Phytoanticipins and (2) Phytoalexins. Phytoanticipins inhibit the microbial actions whereas Phytoalexins are generally antioxidants (Sukalingam et al., 2017, 2018).

Antimicrobials secondary metabolites extracted from plants are grouped into three types; (1) Phenolic compounds (2) Terpenes and (3) Alkaloids. These antimicrobial extracts disrupts cell wall, induce reactive oxygen species production, stops the formation of biofilm, inhibit cell wall construction, inhibit microbial DNA replication, inhibit energy synthesis, and inhibit bacterial toxins to the host (Awolola et al., 2014; Cushnie et al., 2007; El-Adawi, 2012; Ganesan & Xu, 2017b, 2017c; Górniak et al., 2019; Stapleton et al., 2004). In spite of all these effects these antimicrobials also prevent antimicrobial resistance and synergetic to antibiotics, which helps in killing pathogenic organisms.

Below table shows some anti-microbial agents and their functions;

Table 2-10: List of some anti-microbial agents and their respective functions (Ullah & Ali, 2017)

Sr. No	Name of anti-microbial agent	Function
1.	Sulphonamides	Inhibit folate synthesis at initial stages
2.	Amphenicols, e.g. chloroamphenicol	Inhibits the synthesis of protein
3.	Spectinomycin	Inhibits the synthesis of protein
4.	Trimethoprim	Disturbs the tetrahydrofolate synthesis pathway
5.	Tigecycline	Inhibits the synthesis of protein
6.	Erythromycin	
7.	Linezolid	
8.	Doxycycline	
9.	Penicillin	Interfere the synthesis of the bacterial cell wall
10.	Carbapenems	
11.	Gentamicin	Inhibits the synthesis of protein
12.	Quinolones	Blocks bacterial DNA replication
13.	Vancomycine	Inhibit cell wall synthesis
14.	Polymyxin B	Disrupts cell membrane

2.9.1 Antimicrobial mechanism of bioactive compounds

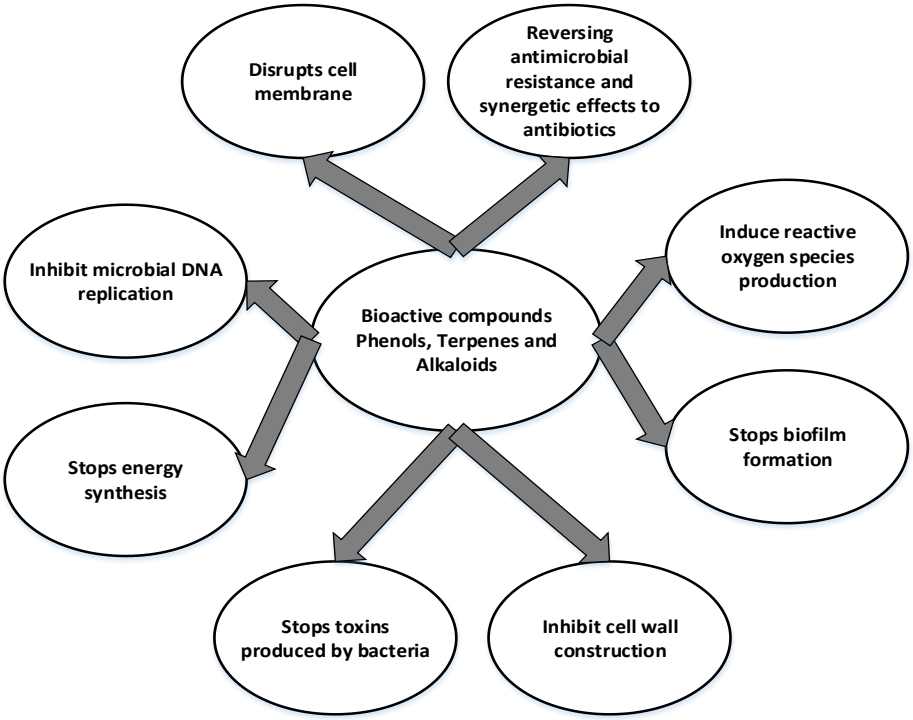


Figure 2-11: Antimicrobial mechanism of bioactive compounds

2.9.1.1 Disrupts cell membrane

Phenolic compounds belong to the family of aromatics containing hydroxyl functional group which when react with the microorganism disrupt their cell wall (Ganesan & Xu, 2017a, 2018). These aromatics are thrown to the microbe's cell surface and thus they cause the disruption to their cell walls (Ganesan & Xu, 2017a). Flavonoids are phenolic compounds which form complex relationship with bacterial cell wall and thus disrupt its structure (Ganesan & Xu, 2017b, 2017c). Some of the flavonoids such as (1), rutin (2), naringenin (3), sophoraflavanone (4), tiliroside (5) and 2, 4, 6-trihydroxy-30-methyl chalcone cause the disruption of S.aureus and S.mutans microbes's (Sanver et al., 2016; Tsuchiya & Iinuma, 2000). Terpenes contains isoprene, which causes the disruption of microbial membranes (Guimarães et al., 2019; Moghrovyan et al., 2019).

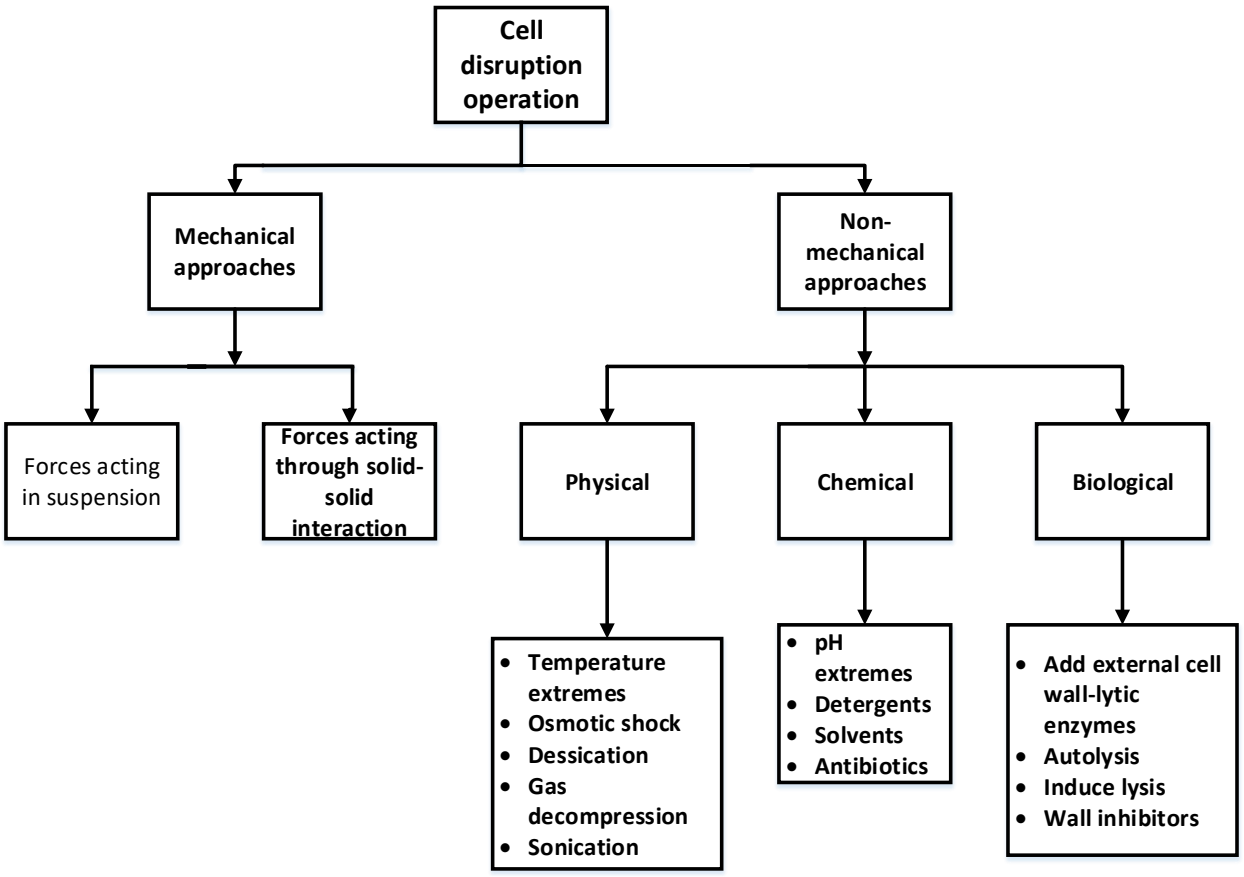


Figure 2-12: Promote cell wall disruption and lysis

2.9.1.2 Reversing antimicrobial resistance and synergetic effects to antibiotics

Disease causing bacteria have resistance against various antibiotics due to different mechanisms. These mechanisms are; (1) resistance through transformation, transduction, and conjugation phenomenon's (2) antibiotics deactivation through the processes of phosphorylation, adenylation, or acetylation (3) bacteria prevent the interaction of drug and antibiotic (4) efflux of the antibiotic from the cell (Bush, 2013; Bush & Fisher, 2011; Munita & Arias, 2016).

2.9.1.3 Induce reactive oxygen species production

Reactive oxygen species are formed by the partial reduction of molecular oxygen that targets the exertion of antimicrobial activity which helps defensing against various microbes. The method of catechins involves augmentation of the production of oxidative stress causes disruption of cell wall (Fathima & Rao, 2016). In another study it was shown that catechins cause disruption of membrane in S.aureus (Górniak et al., 2019).

2.9.1.4 Inhibit biofilm formation

Biofilms developed by bacteria are 100-1000 times more resistant to antimicrobial drugs (Kahaliw et al., 2017). In some studies it was indicated that flavonoids aggregates the multicellular composites and thus inhibit bacteria growth. Flavonoids such as; (1) galangin, (2) isovitexin (3) 3-O-octanoyl-epicatechin and (4) 5, 7, and 40-trihydroxyflavanol cause the aggregation of S. aureus and S. mutans thus inhibiting their growths (Awolola et al., 2014; Cushnie et al., 2007; El-Adawi, 2012; Stapleton et al., 2004).

2.9.1.5 Stops cell wall construction

Bacterial cell wall causes osmoregulation, respiration, transport mechanism, and biosynthesis of lipids. For these functions' membrane health is very important and thus the disruption of membrane leads to bacterial death (Reygaert, 2014).

2.9.1.6 Stops toxins produced by bacteria

Catechins and some other flavonoids cause disruption of bacteria cell wall and in this way inhibits the discharge of toxins (Lee et al., 2011; Shah et al., 2008).

2.9.1.7 Inhibit energy synthesis

Production of energy or ATP is important for the development of bacteria on which living systems depends. Flavonoids disrupts the cell wall of S. aureus (Kuete et al., 2011).

2.9.1.8 Inhibit microbial DNA replication

Alkaloids inhibits the respiration of cell and stops the production of various enzymes that are involved in multiplication of cells (Zielińska et al., 2019). Bioactive compounds present in plants such as quercetin, nobiletin, myricetin, tangeritin, genistein, apigenin, chrysin, kaempferol, and 3, 6, 7, 30, 40-pentahydroxyflavone are DNA disrupters (Plaper et al., 2003; Ulanowska et al., 2006; Verdrengh et al., 2004; Vijayakumar et al., 2018; Wu et al., 2008).

2.9.2 Antimicrobial mechanism of Thymoquinone

Bacterial pathogens are the main causes of respiratory system diseases i.e. pneumonia and bronchitis. Biofilm formation is the important activity of microbes in their virulence strategy. Thymoquinone stops biofilm formation in some bacterial species and inhibit the oxidative activity of microbes present in biofilm that eventually reduces the number of microbes (Khan, 2018).

Since fungal infections are increasing due to immense usage of immunosuppressive chemotherapeutics against malignant diseases and in the transplantation of organs. Thymoquinone is effective against fungus causing pathogens like *Candida albicans* and *Aspergillus fumigatus* (Khan, 2018).

2.9.3 Antimicrobial mechanism of Melanin

Upon infection, melanin formation around a pathogen blocks its proliferation (Nosanchuk & Casadevall, 2006).

2.9.4 Antimicrobial mechanism of P-cymene

P-cymene by accumulating in bacterial membrane and changes its structure. P-cymene has significant impact against protein and cause the death of E.coli (Marchese et al., 2017).

2.9.5 Antimicrobial mechanism of Pinene

Pinene have antimicrobial activity against C. albicans, C. neoformans, R. oryzae and MRSA. The combination a pinene with commercially present antimicrobials are important because they reduce MIC, cause antimicrobial activity and decrease toxicity. Pinene also works against the formation of biofilm (Silva et al., 2012).

2.9.6 Antimicrobial mechanism of Alkaloid

Alkaloids are produced naturally by plants and they protect then against pathogens. Alkaloids disrupt cell membrane of microbes, inhibit cellular division, inhibit efflux pump, and inhibit biofilm formation (Mittal & Jaitak, 2019).

2.9.7 Antimicrobial mechanism of Limonene

Limonene has antibacterial activity with significant effect against bacteria (gram-negative and gram positive) as well as against fungi (Han et al., 2020).

2.9.8 Antimicrobial mechanism of Camphene

Camphene penetrate into bacterial cell membrane and disrupts bacterial metabolic function, and cellular activities (Er et al., 2018).

2.10 TECHNIQUES FOR THE PREPARATION OF *NIGELLA SATIVA*

Preparation steps of *Nigella sativa* in literature against microbes are listed in table below;

Table 2-11: Techniques for the preparation of *Nigella sativa*

Name of material	Methodology	Reference
Nigella sativa	• Dry to remove moisture. • Powdered. • Extraction with petroleum and methanol.	(Bhalani & Shah, 2015)
	• Dry. • Soak in hexane, ethyl acetate and methanol. • Evaporate using rotary evaporator.	(Nawarathne et al., 2019)
	• Air dry. • Soak in water. • Hydro distillation. • Heated to vapor. • Condense. • Extraction.	(Manju et al., 2016)
	• Powder. • Mix in ethanol and water. • Prepare extract with Soxhlet apparatus.	(Liaqat et al., 2018)
	• Extraction with ether.	(Roy et al., 2006)
	• Mixture of *Nigella Sativa* and water.	(Bakathir & Abbas, 2011)

2.11 TECHNIQUES FOR THE PREPARATION OF *CAPSICUM FRUTESCENS L.*

Preparation steps of *Capsicum frutescens L.* in literature against microbes are listed in table below;

Table 2-12: Techniques for the preparation of *Capsicum frutescens L*.

Name of material	Methodology	Reference
Capsicum frutescens L.	• Boil in ethanol. • Triple filter. • Extraction.	(Oguzie et al., 2013)
	• Wash. • Oven dry. • Powder. • Boil. • Filter. • Evaporation.	(Koffi-Nevry et al., 2012)
	• Mixture of *Capsicum Frutescens L*. with silver nitrate, garlic and ginger.	(Otunola et al., 2017)
	• Acetonitrile extract of *C. frutescens.*	(Nascimento et al., 2014)
	• Dry. • Add solvent. • Filter. • Evaporate.	(Doğan et al., 2018)
	• *Capsicum frutescens L.* extract.	(Cao & Zhu, 2007)

MATERIALS AND METHODS

3.1 REAGENTS

Nutrient agar (Chomini et al., 2020) and nutrient broth were used for the growth of both *Pseudomonas aeruginosa* and *Klebsiella species*. Agar and broth were collected from Biotechnology lab, IESE, NUST. Bacteria's were collected from Microbiology lab, IESE, NUST. Plant materials includes *Nigella sativa* and *Capsicum frutescens L* both were purchased from local market. Diclofenac free acid antibiotic was also purchased from local market.

3.2 WASHING AND STERILIZATION OF GLASSWARE

All glassware used in the experiments was washed thoroughly and then sterilized by autoclaving at 121^{o}C and 15 psi pressure for 1 hour and 30 minutes. All glassware was dried in oven at 150^{o}C for 1 hour after sterilization.

Step 1

Step 2

Step 3

Step 4

3.3 PREPARATION OF MEDIA

Nutrient broth and Nutrient agar were prepared by adding 6.5g of broth and 14g of agar in 500 ml of distilled water respectively. Both were then autoclaved at 121^{o}C and 15 psi for 1 hour 30 minutes. For sterility test the broth was placed in incubator at 37^{o}C for 24 hours while agar was poured in petri plated and then placed in incubator at 37^{o}C for 24 hours.

Step 1 Step 2 Step 3

3.4 *NIGELLA SATIVA* AND *CAPSICUM FRUTESCENS L.* COLLECTION AND PREPARATION

N. sativa and *Capsicum frutescens L.* were purchased from the local market. After grinding them manually in a domestic grinder they were allowed to mix separately in distilled water. Stock solutions were made as 2, 5, 7 and 10 g *Nigella sativa* in 20 ml distilled water respectively. Then *N. sativa* and distilled water solution was mix thoroughly on a shaker so that homogenous mixture was obtained same step was performed for *Capsicum frutescens L.* and distilled water solution. After this both are filter one by one in filtration assembly using Whatman filter paper No 1 and then filtered samples was placed in autoclave for sterilization at 121^{o}C and 15 psi for 1 hour and 30 minutes. After this samples are stored at 8^{o}C.

Step 1

Step 2

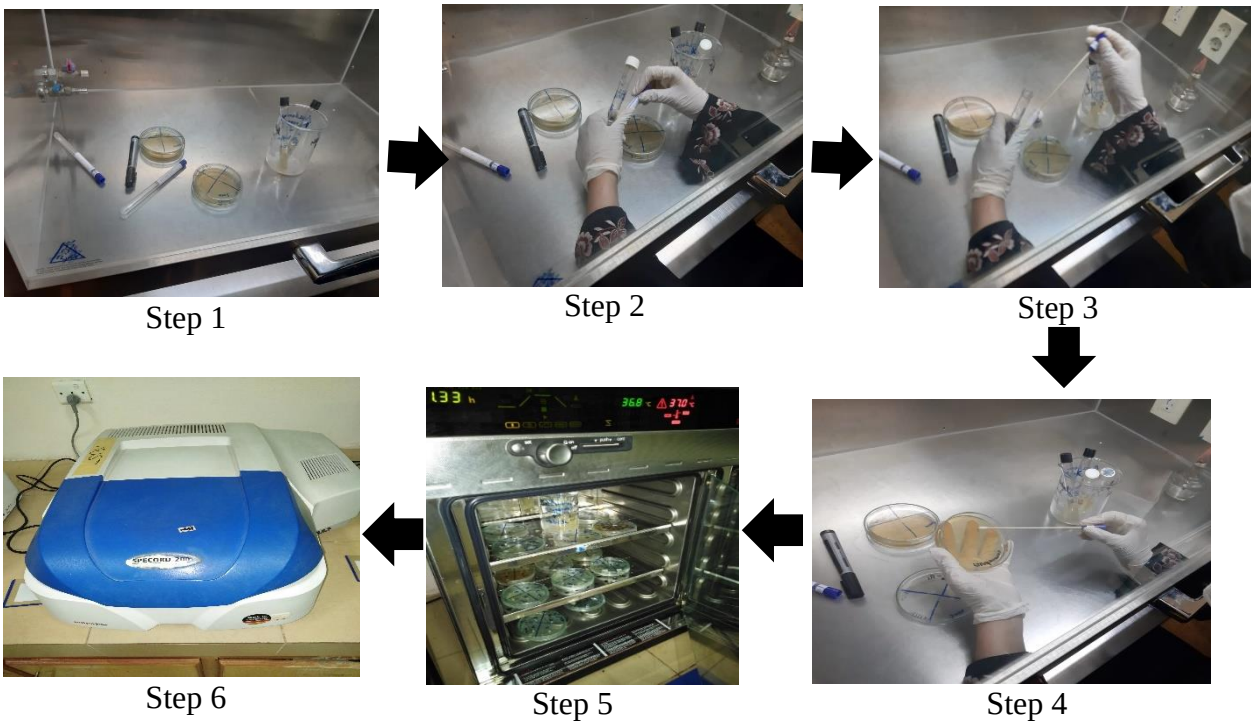
Step 3

Step 4

3.5 BACTERIAL INOCULUM PREPARATION

Pseudomonas aeruginosa and *Klebsiella species* control samples was taken from Microbiology lab of Institute of Environmental Sciences and Engineering, National University of Sciences and Technology, Islamabad Pakistan.

The day prior to test picked isolated colonies of bacteria's and they were allowed to grow 48 hours in 5ml broth medium at 37°C. Standardized the inoculum size by measuring the absorbance at 600nm in spectrophotometer. At the time of test, absorbance was 0.5 at 600 nm.

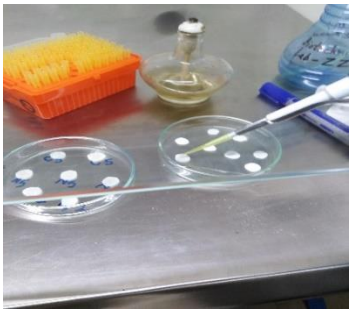


Step 1 Step 2 Step 3

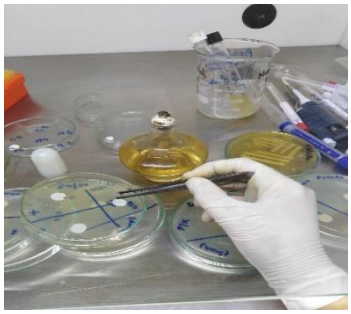
Step 4 Step 5 Step 6

3.6 PREPARATION OF FILTER PAPER DISCS

Through micropipette 5, 10, 15 and 20µl dilutions of respective samples were loaded on filtered paper discs and then discs were allowed to completely dry in laminar flow hood for 30 minutes. After this, discs were stored in refrigerator at 8°C. When the media was poured and bacteria were streaked on media, carefully placed dried discs with sterilized spatula on media and slightly tap it on the media so that the discs makes fully contact with the media.



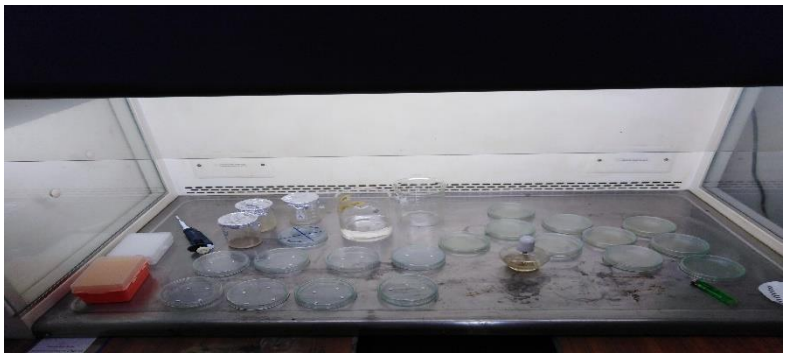
Step 1



Step 2

3.7 POURING OF MEDIA

Prepared nutrient agar was poured carefully on sterilized and autoclaved petri plates in laminar flow. After pouring 150µL nutrient agar on petri plates, agar plates were placed in oven at 37°C for 24 hours for the sterility test. If no bacterial colonies were found on agar plates, then these plates were used for further tests. If slight contamination found on agar plates, then the plates were discarded.



Step 1

Step 2

3.8 STREAKING OF BACTERIA

Bacterial single colony was picked and were streaked on petri plate by sterilized swabs. *Pseudomonas aeruginosa* and *Klebsiella species* were streaked on separate plates. After this inhibition zones were measured. On the maximum zone of inhibition conditions both bacterial colonies were streaked one by one on single agar plate and combine bacterial effect was measured.

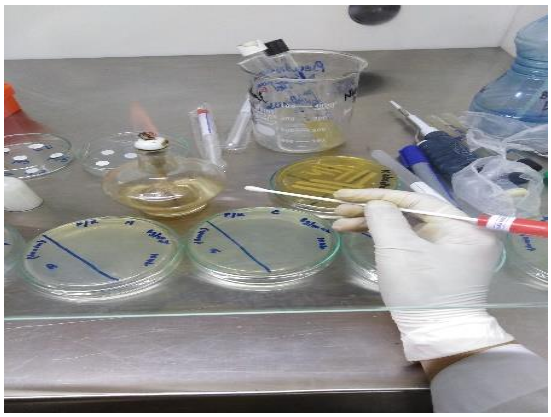


Figure 3-1: Streaking

3.9 LOADING OF FILTER PAPER DISCS

When the agar plates were prepared then prepared discs were placed on them. Each plate was divided into 4 regions. One first region *Nigella sativa* disc, on second disc *Capsicum Frutescens L.*, on third diclofenac free acid antibiotic as a positive control and on four region distilled water disc was placed. After placing all discs, they were allowed to have fully contact with the media by pressing them slightly. Then these petri plates were placed in Oven at 37^{o}C for 24 hours to check the inhibition zones.

3.10 KIRBY BAUER METHOD OF PLANT MATERIAL SUSCEPTIBILITY TESTING (DISC DIFFUSION METHOD)

Disc diffusion method was used for the evaluation of antimicrobial effects of *Nigella sativa* and *Capsicum frutescens L*. 2, 5, 7, 10g per 20ml distilled water stock solution of both plants were prepared and these stock solution further dilutions of 5,10,15 and 20 µl were poured on prepared discs by micropipette as shown in table below;

Table 3-1: Disc diffusion method

Organism	Plants	Stock solution g/20ml	Dilutions µl
Pseudomonas aeruginosa	*Nigella sativa*	2	5 10 15 20
		5	5 10 15 20
		7	5 10 15 20
	Capsicum frutescens L.	2	5 10 15 20
		5	5 10 15 20
		7	5 10 15 20
Klebsiella species	*Nigella sativa*	2	5 10 15 20

Organism	Plants	Stock solution g/20ml	Dilutions µl
		5	5 10 15 20
		7	5 10 15 20
		10	5 10 15 20
	Capsicum frutescens L.	2	5 10 15 20
		5	5 10 15 20
		7	5 10 15 20
		10	5 10 15 20
Pseudomonas aeruginosa + *Klebsiella species*	*Nigella sativa*	5	10
	Capsicum frutescens L.	5	10

3.11 FTIR ANALYSIS

FTIR analysis of plant material and distilled water solution was conducted for the determination of active antimicrobial groups in them. FTIR is rapid technique with minimum sample preparation, economical, simple handling and require less sample compared to GC-MS (Aysal et al., 2007; Nivetha & Prasanna, 2016).

Step 1

Step 2

RESULTS AND DISCUSSIONS

4.1 FLOW DIAGRAM FOR THE DATABASE SEARCH OF PUBLICATIONS

Firstly 480 studies abstracts were reviewed then from these 360 studies included for full text review, from these 360; 150 studies were excluded because no relevant synergy was reported in them and from 360, 245 studies are included in this research in which 35 studies were added from conference proceeding, 15 were added through reference reviews and 195 were added from google scholar.

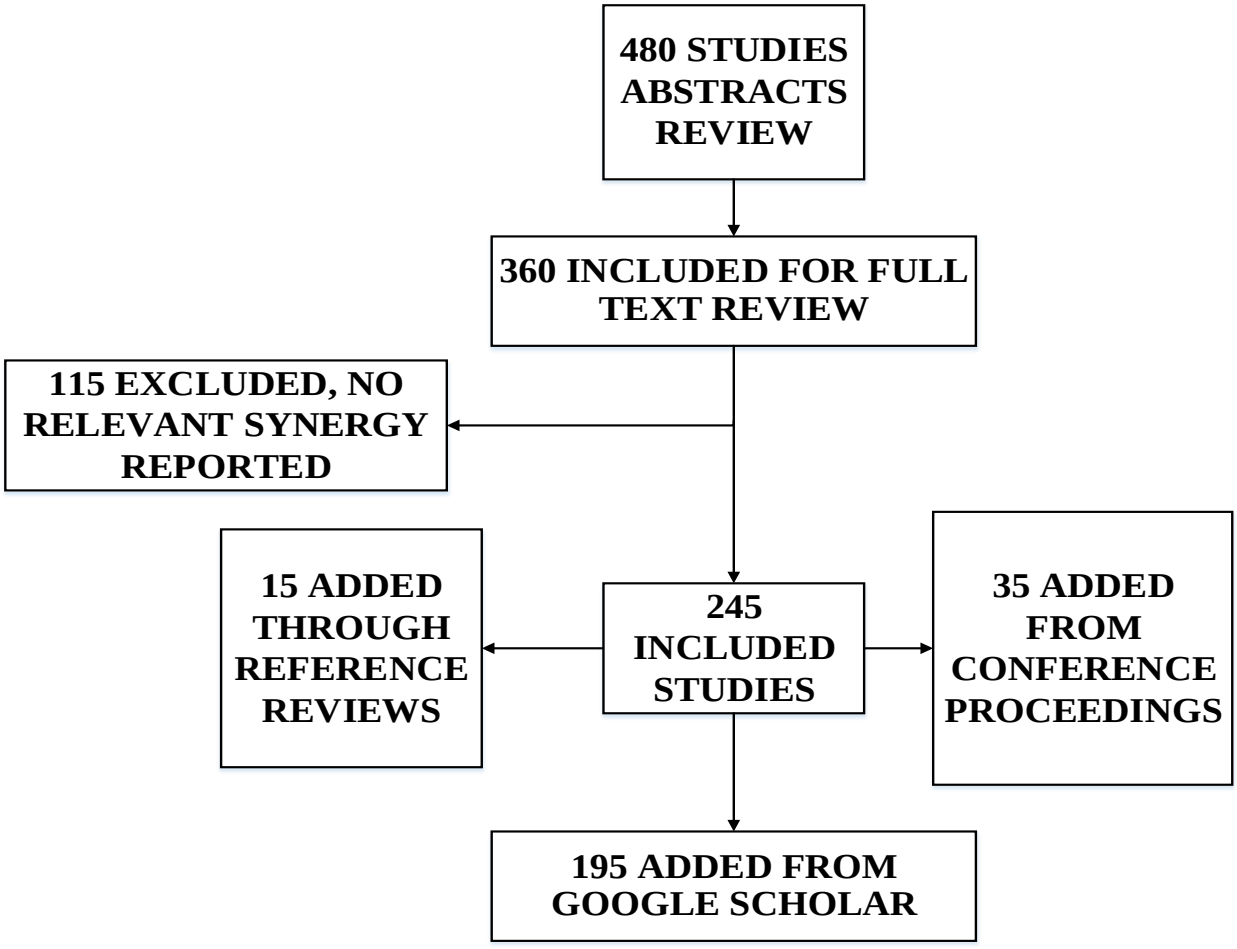


Figure 4-1: Flow diagram database search of publications

4.2 COMPARATIVE ANALYSIS OF USAGE OF DIFFERENT SUBSTANCES TO CONTROL MICROBIAL INFECTIONS

From meta-analysis it was concluded that previous research works were on plant extracts, plant materials or on plant derived products as shown in table below;

Table 4-1: Comparative analysis of usage of different substances to control microbial infections

Sr No.	Potential component	No of studies	Relative efficiencies (%)
1.	Plant extracts (Essential oil, Coumarine, Vanillic acid, Naphthoquinones, Allicin, garlic acid, Amorphastibol and Alkaloids etc)	98	94
2.	Plant materials (*Nigella sativa*, *Capsicum frutescens* L., *Aloe*, *Malus domestica*, *Ocimum basilicum*, *Piper nigrum* and *Cyanococcus* etc)	74	75
3.	Plant derived products (Antibiotics and related substances)	93	90

4.3 ANALYSIS OF WORLDWIDE MORTALITY DUE TO BACTERIAL SPECIES

Among different bacterial species 61% of worldwide deaths are due to *Pseudomonas aeruginosa* and 69% of worldwide deaths are due to *Klebsiella species*. This high death rate urges the researcher of present study to find effective antibacterial solution against *Pseudomonas aeruginosa* and *Klebsiella species* infections (Chessa et al., 2015; Dutta et al., 2013; Ko et al., 2002; Linden et al., 2003; Ramirez-Garcia et al., 2016; Sati et al., 2019; Siegman-Igra et al., 2002; Van Delden & Iglewski, 1998; Younes et al., 2016).

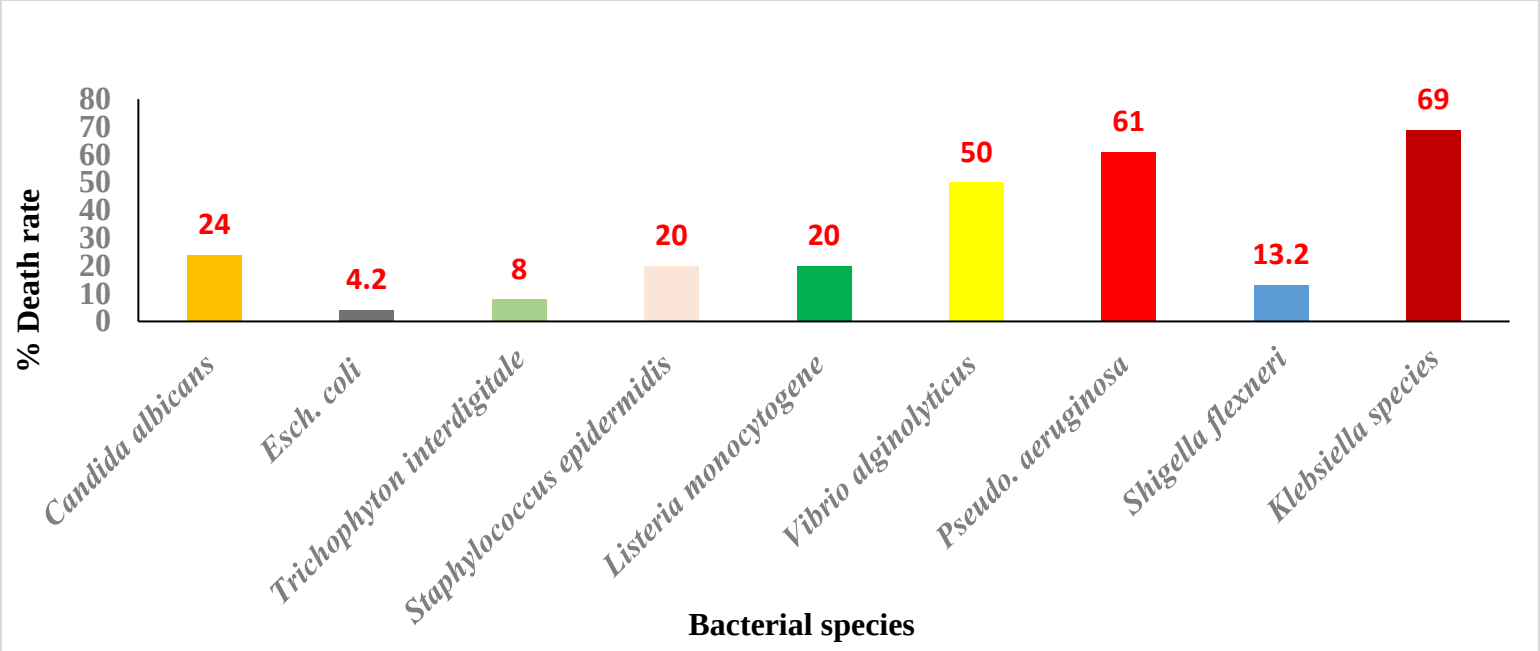


Figure 4-2: Analysis of worldwide mortality due to bacterial species

4.4 INFECTIOUS DISEASES CURED BY *NIGELLA SATIVA* AND *CAPSICUM FRUTESCENS* L.

N. sativa and *Capsicum frutescens* L. can cure cancer, stiff joints, cough, headache, skin infection, hair whitening, osteoarthritis, blood pressure, they have anti-viral, anti-fungal and anti-microbial properties (Bakhtiar & Sardo; Gbadamosi & Erinoso, 2016; Hussein, 2015; Kunnumakkara et al., 2009; Ramzan et al., 2017; Saad, 2015; Sahai et al.; Saleh et al., 2018; Singh, 2008; Taha et al., 2019) as shown in table below:

Table 4-2: Infectious diseases cured by *Nigella sativa* and *Capsicum frutescens* l.

Sr. No	Diseases	*Nigella sativa*	*Capsicum frutescens* L.
1.	Cancer	✔	✔
2.	Stiff joints	✔	✔
3.	Cough	✔	✔

Sr. No	Diseases	*Nigella sativa*	*Capsicum frutescens* L.
4.	Headache	✔	✔
5.	Skin infection	✔	✔
6.	Hair whitening	✔	✔
7.	Osteoarthritis	✔	✔
8.	Blood pressure	✔	✔
9.	Anti-viral properties	✔	✔
10.	Anti-fungal properties	✔	✔
11.	Anti-microbial properties	✔	✔

4.5 GROWTH OF BACTERIAL SPECIES

After collecting bacterial species from controlled environment inoculum size was standardized by measuring the absorbance at 600nm in spectrophotometer. At the time of test, absorbance was 0.5 at 600 nm.

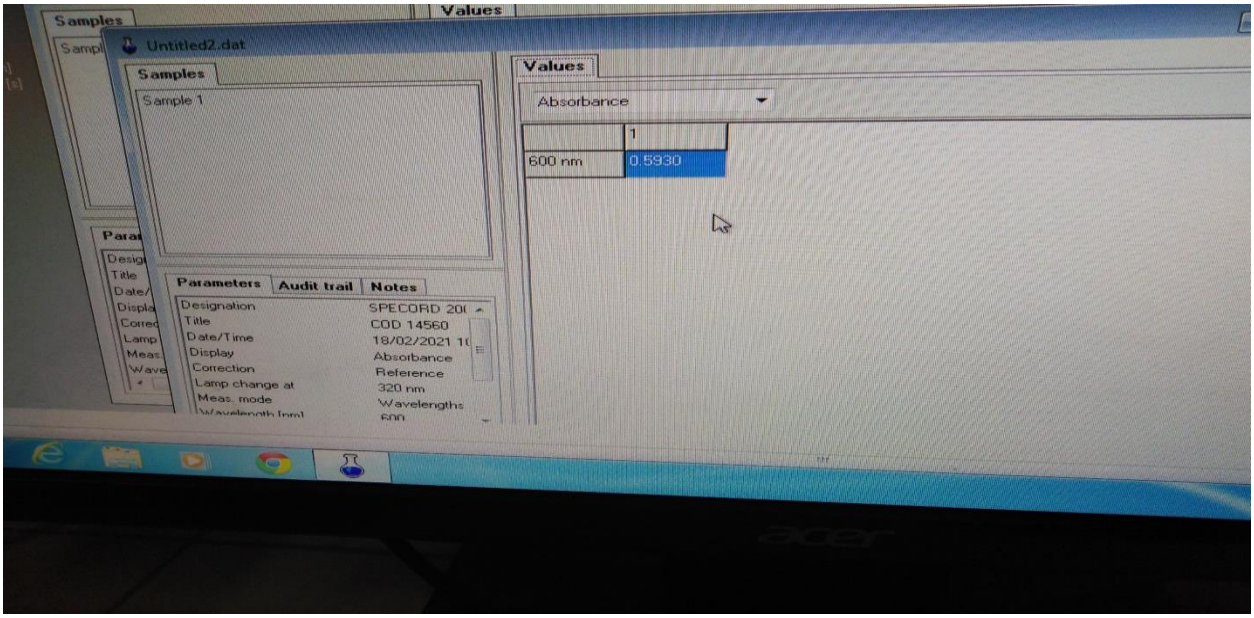


Figure 4-3: 0.5 absorbance at spectrophotometer

When the bacterial species are grown dip sterile swab in nutrient broth containing bacteria's and streak on agar plates.

Figure 4-4: Growth of Pseudomonas aeruginosa and Klebsiella specie

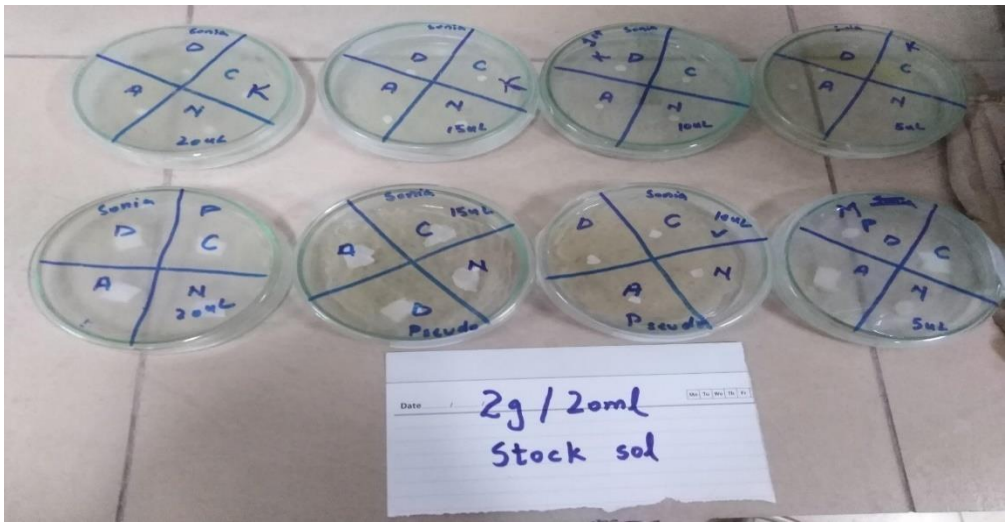
4.6 DISC DIFFUSION METHOD

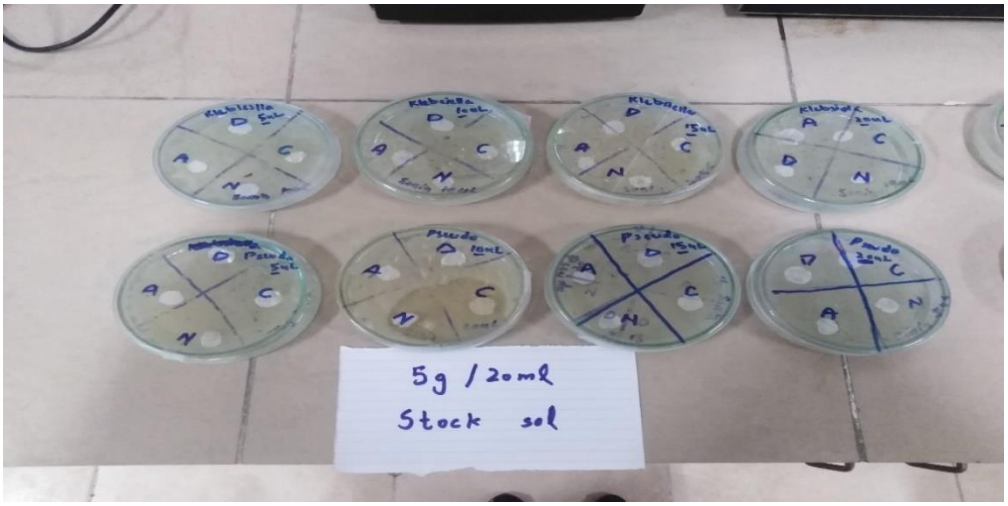
- For the Pseudomonas aeruginosa observed zone of inhibition was 30mm and 25mm by 5g/20ml *Capsicum frutescens L*. *Nigella sativa* for 10uL dilution respectively.
- For *Klebsiella specie* no zone of inhibition was observed by *Capsicum frutescens L.* while 1mm zone of inhibition was observed by 7g/20ml *Nigella sativa* for 20uL dilution.

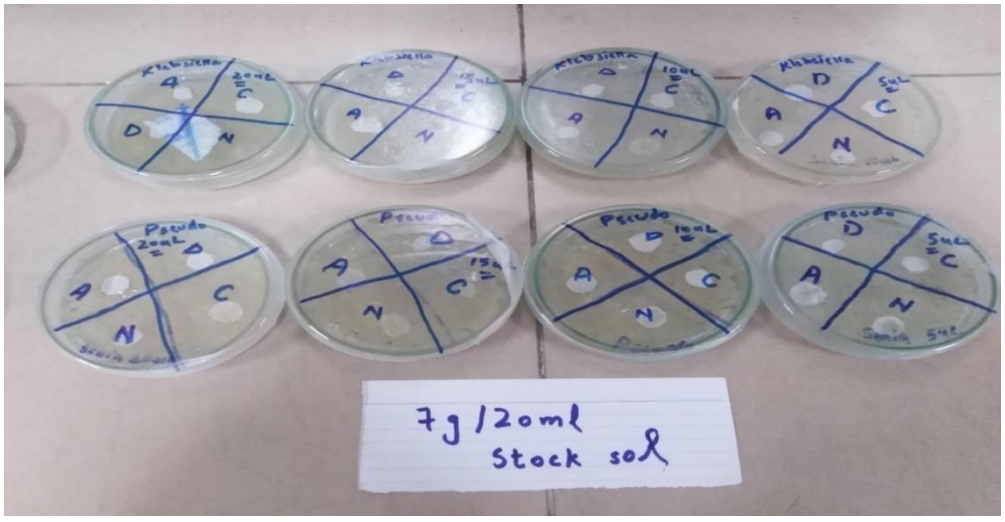
- Positive results of *Nigella sativa* and *Capsicum frutescens L*. were evaluated against both bacteria streaked on single petri plate and by *Nigella sativa* 20mm zone of inhibition was observed while no zone of inhibition was observed by *Capsicum frutescens L* as shown in table below;

Table 4-3: Observed outcomes

Organism	Plants	Stock solution g/20ml	Dilutions µl	Zones of inhibition (mm)
Pseudomonas aeruginosa	*Nigella sativa*	5	10	25
	Capsicum frutescens L.	5	10	30
Klebsiella specie	*Nigella sativa*	7	20	1
	Capsicum frutescens L.	7	20	-
Pseudomonas aeruginosa+ Klebsiella specie	*Nigella sativa*	5	10	20
	Capsicum frutescens L.	5	10	-




5g /20ml
Stock sol


7g /20ml
Stock sol

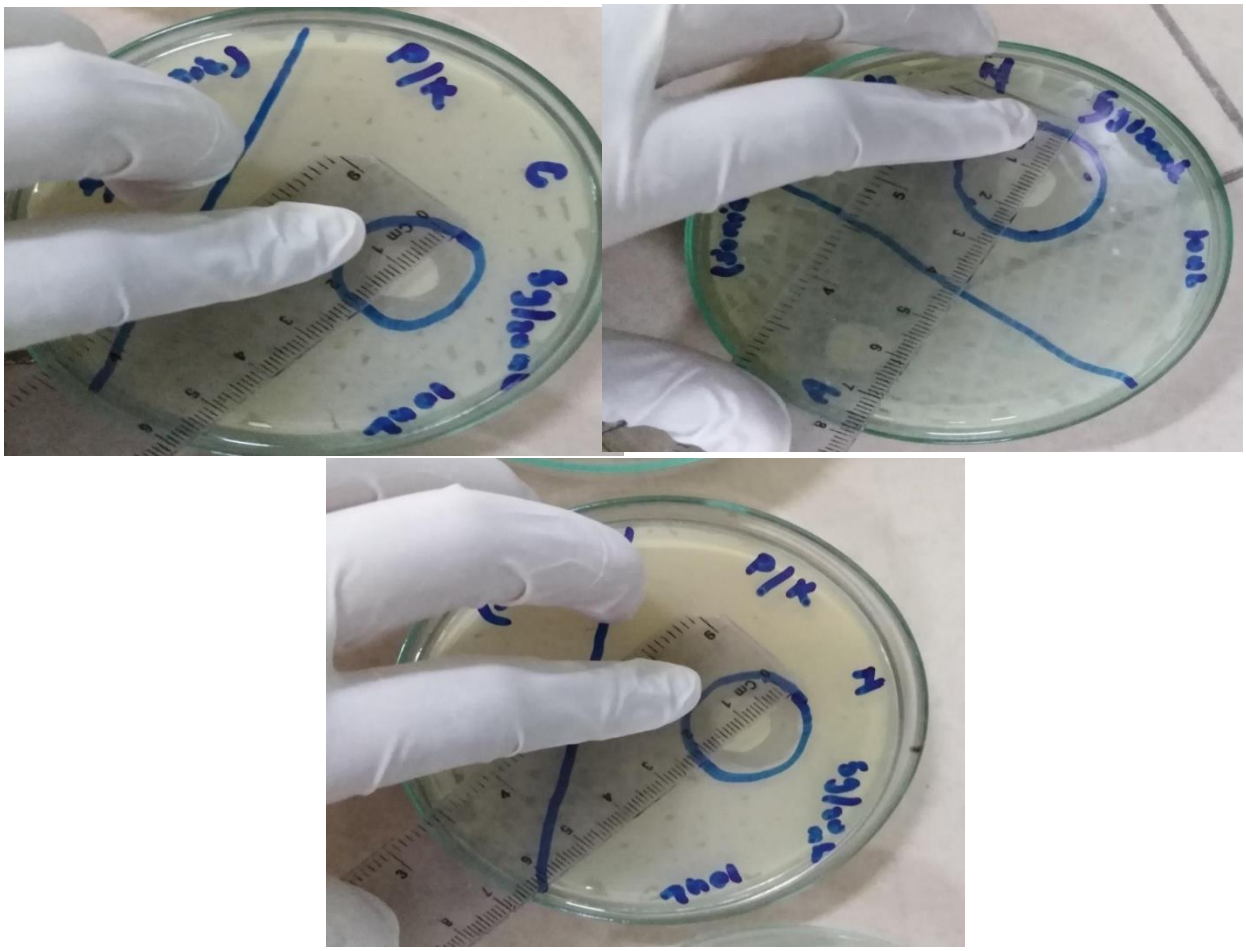


Figure 4-5: Measurement of zone of inhibition

4.7 INTERPRETATION AND REPORTING OF THE RESULTS

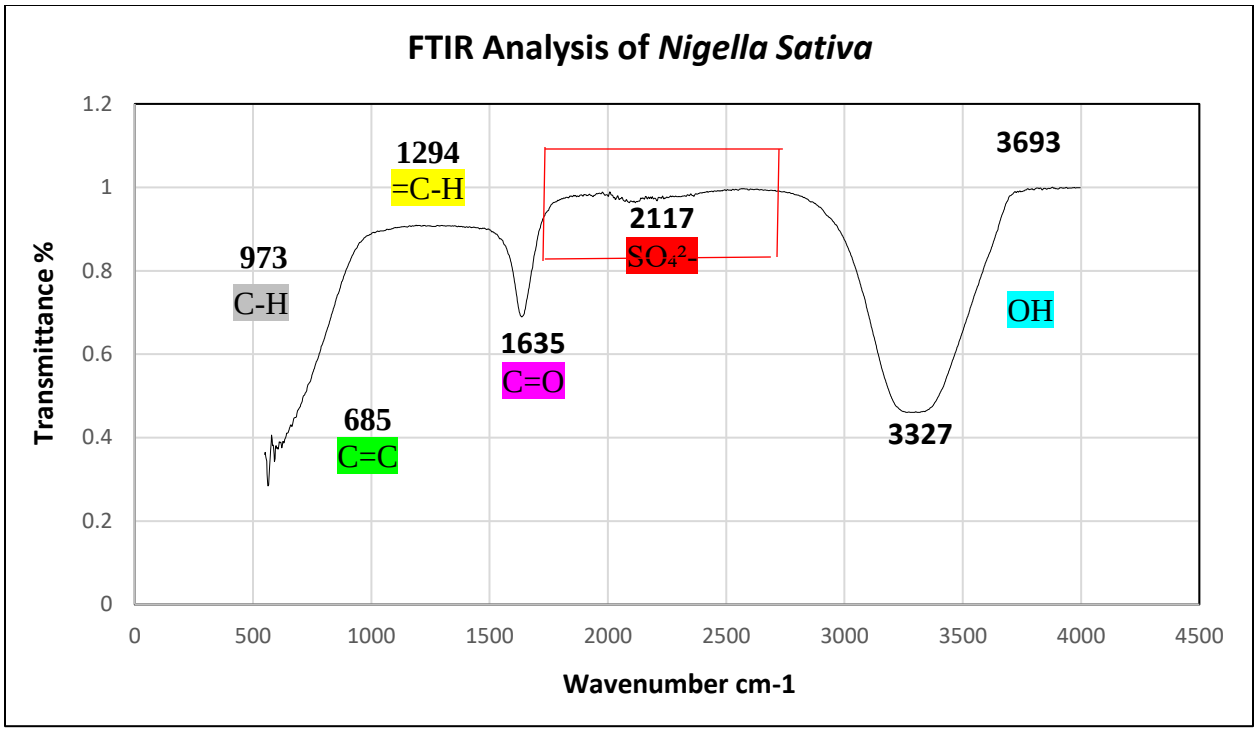
Using the published Clinical & Laboratory Standards Institute **(**CLSI) guidelines, determine the susceptibility or resistance of the organism to each plant material. For each plant material, indicate on the recording sheet whether the zone size is susceptible (S), intermediate (I), or resistant (R) based on the interpretation chart. Susceptible means that the plant material is effective against bacterial species, intermediate means higher dose is needed to prevent bacterial growth while resistant means that the plant material is ineffective against bacterial species. Table below shows that the 20mm zone of inhibition of *N. sativa* has a susceptible effect.

Table 4-4: Pseudomonas aeruginosa and Klebsiella species recommended antimicrobial disks interpretative zone sizes (Hudzicki, 2009)

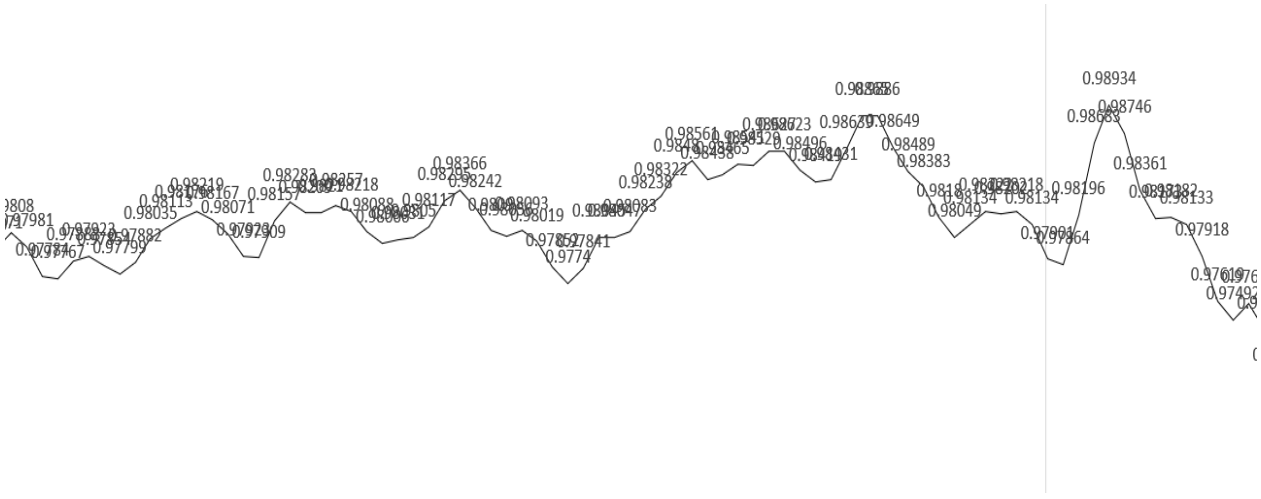
	Resistant	Intermediate	Sensitive	Result
Amikacin	≤14	15-16	≥17	**Therapeutic success**
Cefoperazone	≤15	16-20	≥21	**Uncertain therapeutic effect**
Cefotaxime	≤14	15-22	≥23	**Uncertain therapeutic effect**
Gentamicin	≤12	13-14	≥15	**Therapeutic success**
Piperacillin	≤17	-	≥18	**Therapeutic success**
Tetracycline	≤14	15-18	≥19	**Therapeutic success**
Ticarcillin	≤14	-	≥15	**Therapeutic success**
Tobramycin	≤12	13-14	≥15	**Therapeutic success**

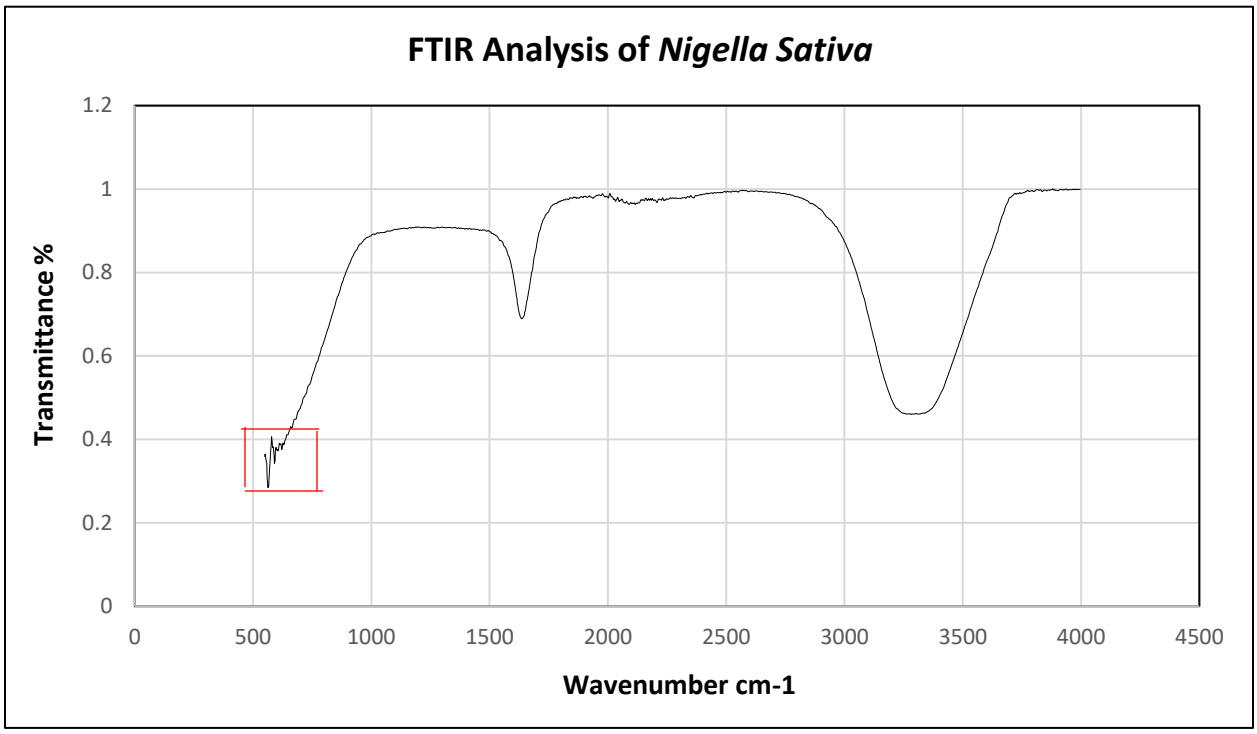
4.8 FTIR ANALYSIS OF *NIGELLA SATIVA* AND *CAPSICUM FRUTESENCE L.*

The FTIR graph shows that the peaks for the plant samples was in the range of 4000–500 cm^{-1}. Spectra of *N. sativa* and *Capsicum* were analysed and the information extracted was as follows; sharp peak at 1636 cm^{-1} is of aldehyde carbonyl C=O (Masyithah et al., 2017). This main peak corresponds to high levels of carboxylic acid in *N. sativa* and *Capsicum*. The peak at 2117 cm^{-1} is assigned to the sulphate group (Prasad et al., 2005). 1294 cm^{-1} peak is attributed to the CH_2 alkanes (Li et al., 2013). The peak at 973 cm^{-1} is assigned to the ethane C-H bending vibration absorption (Li et al., 2013). The peak at 685 cm^{-1} corresponds to alkenes (Li et al., 2013). The plant materials exhibit much complexity and diversity in minor peaks. However, the spectra for both the samples in the range of 4000–500 cm^{-1} are quite similar.



Red box spectrum is shown below:





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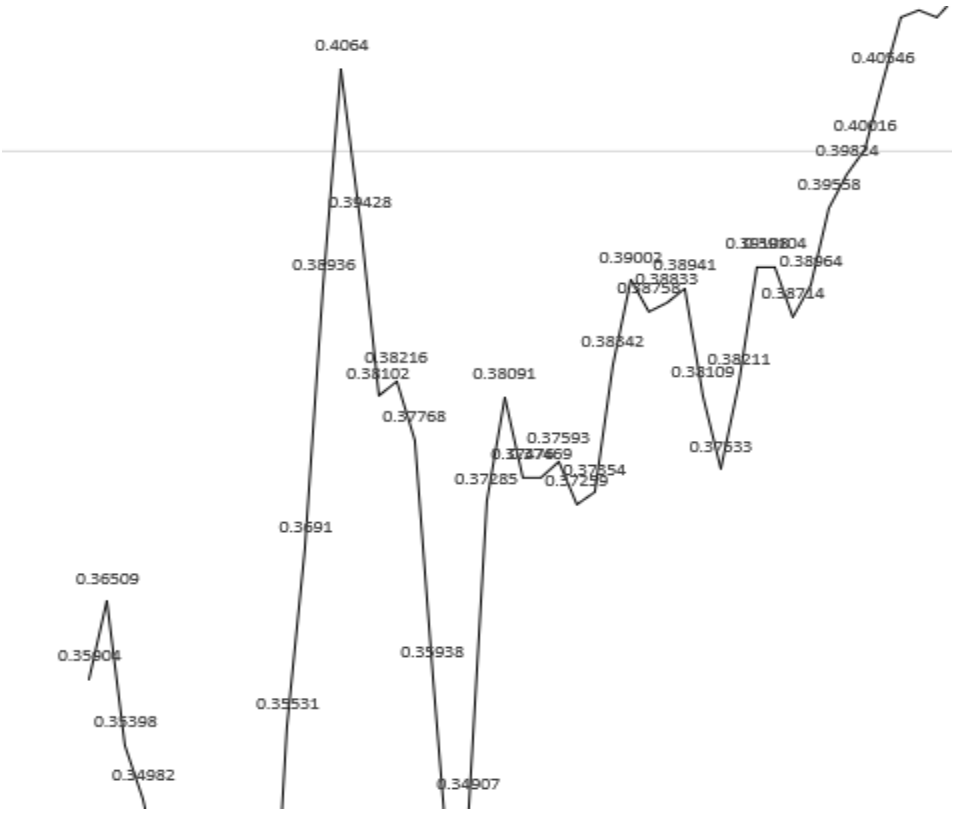

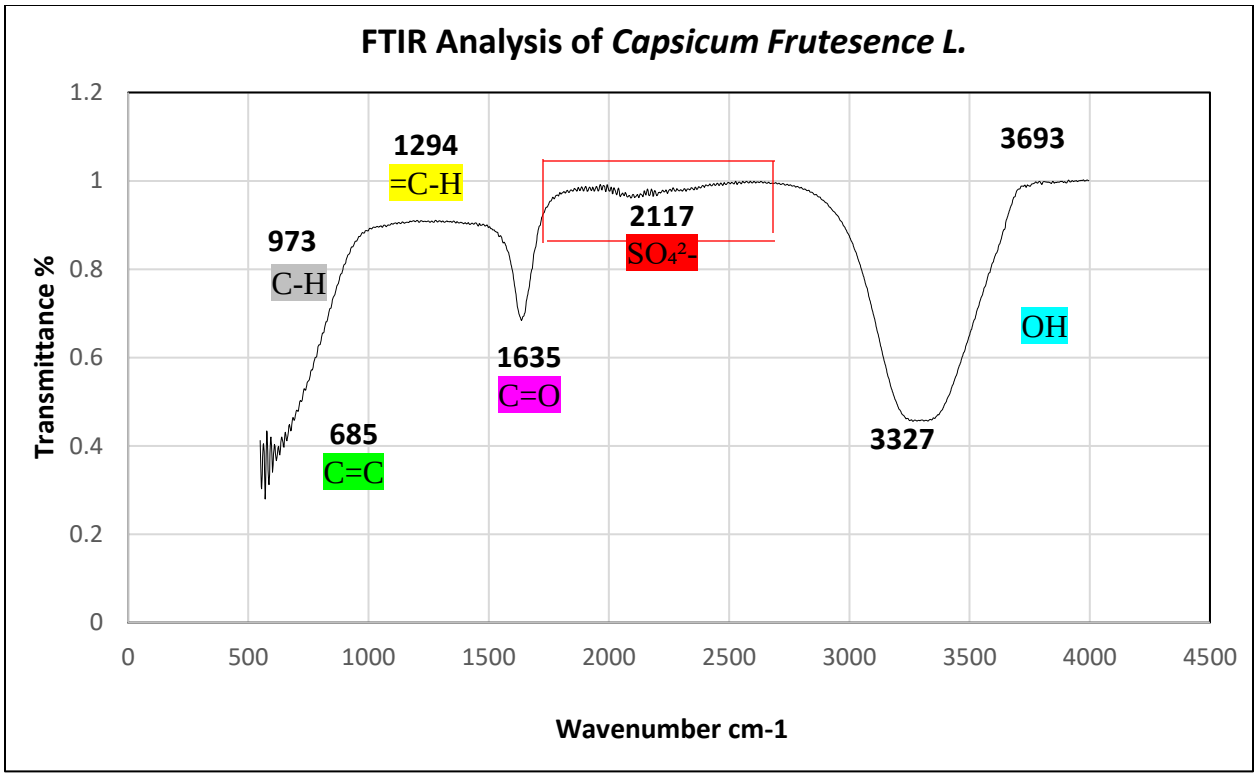

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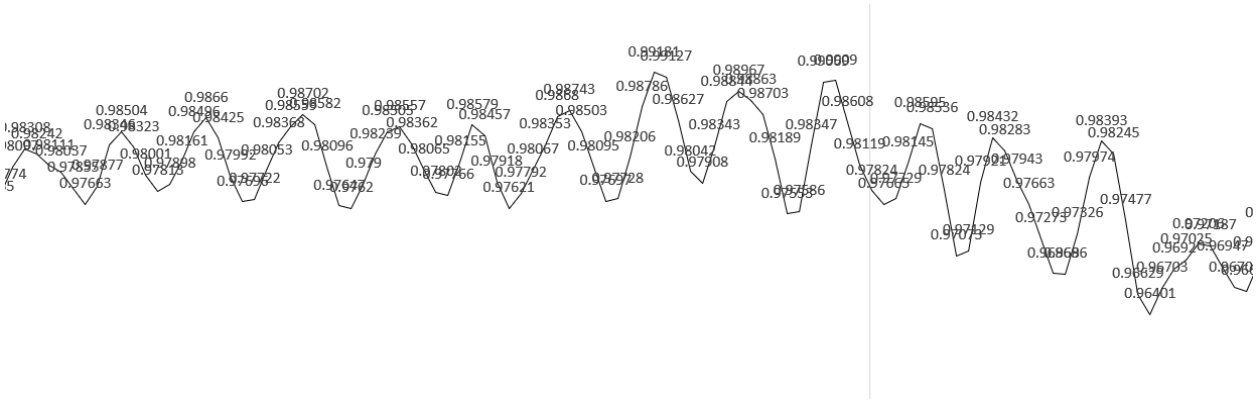

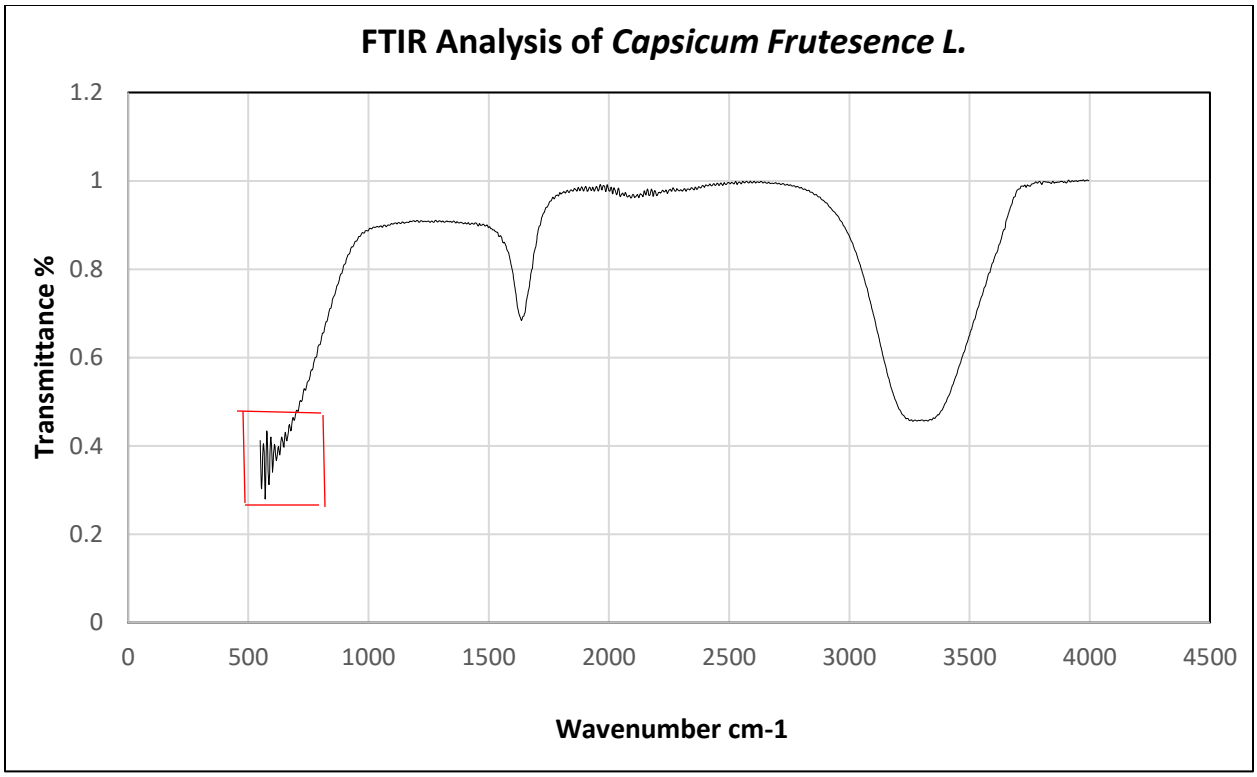

Red box spectrum is shown below:

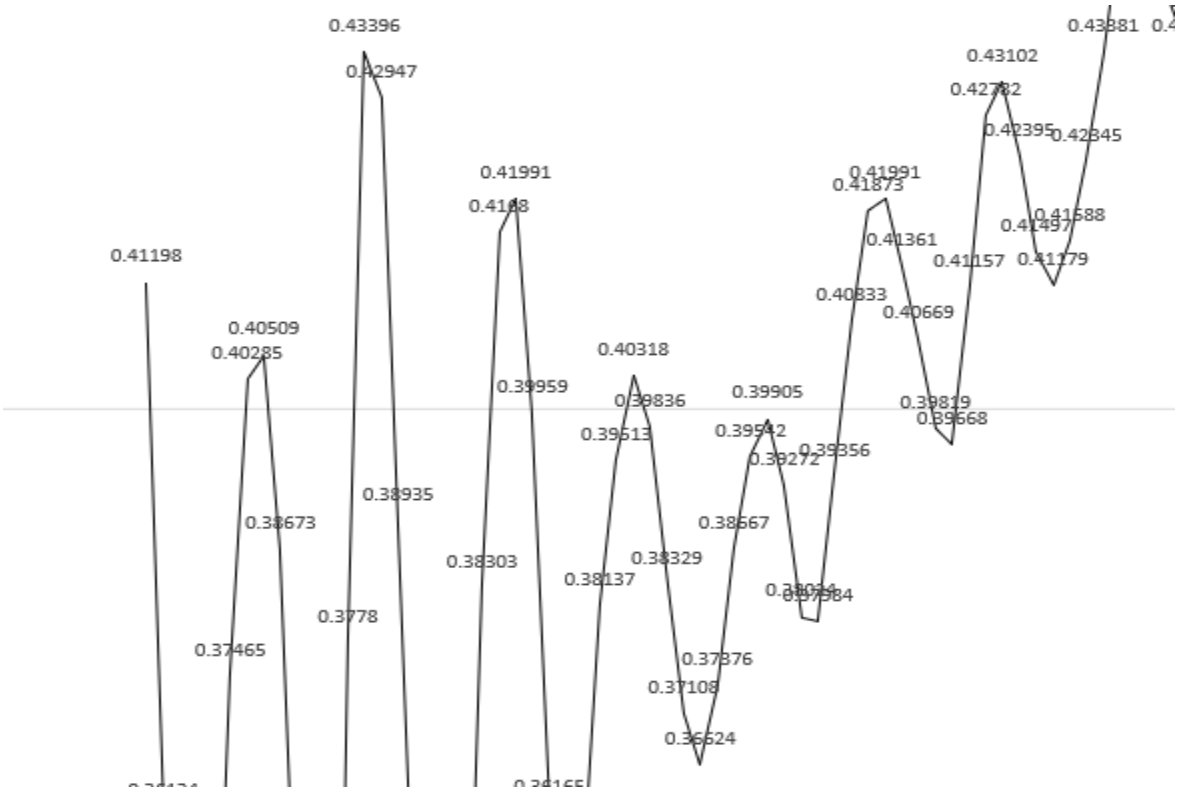

Table 4-5: FTIR analysis of *N. sativa* and *Capsicum frutescens L*.

Sr No.	Peak value	Bond	Functional group	Pharmocalogical Activity	Reference
1.	2117	SO_4^{2-}	sulphate group	Sulphated flavonoids have anticoagulant, anti-inflammatory, and antitumor activities.	(Barron et al., 1988; Calzia et al., 2015; Gledhill et al., 2007; Guglielmone et al., 2005; Teles et al., 2015)
2.	1635	C=O	aldehyde carbonyl	C=O are the carboxylic acids and their derivatives. These are used in pharmaceutical drugs and can also be used antimicrobials.	(Badea & Radu, 2018)
3.	1294	=C-H	alkanes	Alkanes have little biological activity.	(Holla et al., 2001)
4.	973	C-H	ethane	-	
5.	685	C=C	alkenes	Alkenes have little biological activity.	(Tsukamoto et al., 1994)

A slight difference in the minor peaks can be observed in FTIR graphs of *Nigella sativa* and *Capsicum frutescens* L. however no significant difference is seen in overall spectrum.

Presently the major cause of restlessness in the whole world is the spreading of infectious diseases. So, there is a need to save human beings by adopting suitable preventive measures such as using antimicrobial agents on regular basis. Therefore, it is proposed in this work that *Nigella Sativa* should be considered against different microbial infections, reasoning the raw material cost is low as well as it is easily available to every human being.

Most plant materials are active against only gram-positive bacteria while some are active against both gram positive and gram-negative bacteria. In present study *Capsicum frutescens* L. does not show inhibition zone when combined bacterial species were streaked on a single plate it may be due to the fact that *Capsicum frutescens* L. is not much effective against gram negative bacteria (Koffi-Nevry et al., 2012). A.R. McCutcheona in his paper proved that the presence and absence of light also effects the activity of plant materials on bacteria. This can be a reason that *Capsicum frutescens* L. didn't show any antibacterial effect (McCutcheon et al., 1992). Neelam in her paper showed that n-hexane and chloroform extracts of *Capsicum frutescens* L. are effective against *Pseudomonas aeruginosa* and *Klebsiella pneumonae* (Gurnani et al., 2016). Morsi in his paper proved that crude alkaloids and water extracts of *Nigella sativa* have huge effect against gram negative bacteria (Morsi, 2000). Mashhad in his paper showed that aqueous extract of *N. sativa* did not show any effect against *Candida albicans*, *Staphylococcus aureus* [CPSA] and Pseudomonas aeruginosa but other extracts showed significant effect (Mashhadian & Rakhshandeh, 2005). Emeka et al. in his paper showed that *Nigella sativa* seeds oil have antibacterial effects (Emeka et al., 2015).

These variations in the results are due to different preparation techniques used in these papers and due to different environmental conditions.

4.5 COST ESTIMATION

Table below shows the cost of different antibiotics consumed in comparison with *Pseudomonas aeruginosa* and *Klebsiella specie.* The associated cost of *Nigella sativa* and *Capsicum frutescens* L. can be seen significantly lower in prices. This shows that *Nigella sativa* and *Capsicum frutescens L*. are much economical as compared to market available antibiotics.

Table 4-6: Cost estimation

Antibiotics	**Price (Rs. /Pack)**	**Plants**	**Price (Rs. /kg)**
Amikacin	360	*Nigella sativa*	90
Cefoperazone	225	*Capsicum Frutescens L*.	100
Cefotaxime	110		

Antibiotics	**Price (Rs. /Pack)**	**Plants**	**Price (Rs. /kg)**
Gentamicin	258		
Piperacillin	807		
Tetracycline	801		
Ticarcillin	2720		
Tobramycin	152		

CONCLUSIONS AND RECOMMENDATIONS

- Meta-analysis depicted that gram-negative bacteria are resistant to multiple drugs and are increasingly resistant to most available antibiotics.
- Through extensive meta-analysis it was found that gram-negative bacterial species i.e. *Pseudomonas aeruginosa* and *Klebsiella species* account for worldwide mortality rates of 61 and 69%, respectively
- For the *Pseudomonas aeruginosa* observed zone of inhibition was 30mm and 25mm by 5g/20ml *Capsicum frutescens L*. *Nigella sativa*, respectively for 10 µL dilution.
- For *Klebsiella specie* no zone of inhibition was observed by *Capsicum frutescens L.* while 1mm zone of inhibition was observed by 7g/20ml *Nigella sativa* for 20 µL dilution.
- Positive results of *Nigella sativa* and *Capsicum frutescens L*. were evaluated against both bacteria streaked on single petri plate and by *Nigella sativa* 20mm zone of inhibition was observed while no zone of inhibition was observed by *Capsicum frutescens L.* This 20mm zone of inhibition showed susceptible results in Amikacin, Gentamicin, Piperacillin, Tetracycline, Ticarcillin and in Tobramycin antibiotics. While has intermediate effect in Cefoperazone and in Cefotaxime antibiotics. Susceptible results shows the therapeutic success in the field of pharmacology.
- FTIR analysis of *Nigella sativa* and *Capsicum frutescens L.* showed the presence of alcohol or phenol, sulphate group, major peak of aldehyde carbonyl, alkanes, ethane and alkenes. Alcohol or phenol and sulphate flavonoids have anticoagulant, anti-inflammatory, and antitumor activities. Carboxylic acids and their derivatives are used in pharmaceutical drugs and can also be used as antimicrobials. While Alkanes and Alkenes have little biological activity.
- *Capsicum frutescens L.* did not show inhibition zone when combined bacterial species were streaked on a single plate. It may be due to the fact that *Capsicum frutescens L*. is not much effective against gram negative bacteria. Also, various other factors can be accounted for such as presence and absence of light also effects the antibacterial activity. These variations in the results as compared to previous literature are due to different preparation techniques used in these papers and due to different environmental conditions.

- The results indicated that *Nigella sativa* is more effective than *Capsicum frutescens* L. against combine bacterial species. Thus, *N. sativa* can be used as an effective antimicrobial agent against selected bacterial infections.
- Further *N. sativa* effect on other bacterial species should be evaluated in future.

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