Republic of Iraq
Ministry of Higher Education
and Scientific Research
University of Diyala
College of Medicine

Anti- Cancer and Acute Activities with Heterocyclic Core

A Thesis Submitted to
the Council of the College of Medicine- University of Diyala in Partial Fulfillment of the Requirements for the Master Degree of Science in Medical Microbiology

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1442AH **2020AD**

بسم الله الرحمن الرحيم

﴿يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنكم وَالَّذِينَ أُوتوا الْعِلْم
دَرَجَاتٍ وَاللَّهُ بِمَا تَعْمَلونَ خَبِيرٌ﴾

صدق الله العلي العظيم

سورة المجادلة/الآية 11

Certificate

We, the examining committee certify that we have read this thesis entitled **Anti- Cancer and Acute Activities with Heterocyclic Core** and examined the MSc. student **Yaseen Mohsin Azeez** in its contents, and that in our opinion is accepted as a thesis for the degree of Master in Medical Microbiology.

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Dedication

To the soul of my father …Allah overwhelmed him with His mercy.

To my mother……. God extended her life.

To the one who inhabits my heart and fills my life with joy and pleasure... who supported me with all strength, stood by my side always and bears the hardships of my studies…… My dear wife

To the shining stars in the sky of My life …. My sisters and my dear brother

To the pure, kind hearts and the innocent souls, and the winds of my life, my heart and happiness… My dear children

Acknowledgements

Praise be to Allah, the Lord of the worlds, and the prayer and peace upon the messenger, mercy to the worlds, our prophet Muhammad, and to the his family of the good.

Words cannot express my sincere gratitude and appreciation to the supervisor **Assistant Professor Dr.Walaa Najm Abood** for her help, great interest, kindness and supportive advice in this work. I am very grateful to her for continuous encouragement and support during the completion of the work. Calling on God Almighty to give his a long health and wellness.

My sincere gratitude and appreciation to the supervisor **Assistant Professor Dr. Fadhil Lafta Faraj** for his help, kindness and supportive advice in this work. I am very grateful to him for his continuous encouragement and support during the completion of the work. Calling on God Almighty to give him a long health and wellness.

I would like to extend my thanks and appreciation to the CAC Center for their continued willingness to help me during this study, especially (**Dr. Ahmed Fadhil Al Shannon)**, to assist me in supporting the second part of the research.

I would like to express my sincere thanks to the **head of the Department of Medical Microbiology/College of Medicine/Diyala University and all the teaching staff of the department** for their generous help and support during the time of my studies.

Special thanks are due to Dean of the College of Medicine/Diyala University **Professor Dr. Ismeel Ibrahim Latif**

Last but not least, my thanks and appreciation to all my friends and colleagues for supporting me during my studies and everyone who helped me .

Declaration

I declare that this thesis was prepared under my supervision at the Department of Medical Microbiology / College of Medicine / University of Diyala , in partial fulfilment of the requirements for the degree of Master in Medical Microbiology.

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In view of the available recommendations, I forward this thesis for debate by the examination committee.

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جمهورية العراق
وزاره التعليم العالي والبحث العلمي
جامعة ديالى
كلية الطب

مضاد السرطان والأنشطة الحادة مع جوهر حلقي غير متجانس

رسالة مقدمة إلى كلية الطب بجامعة ديالى
كجزء من متطلبات درجة الماجستير في علم الأحياء المهجرية الطبية

من قبل

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الملخص:

تم اختبارقاعده الاندول الجديده المضاده للسرطان والحادة السميه كمضاد للاكسدة ومضاد للاورام على نوعين من خلايا سرطان الثدي CAM-1 MCF-7 كما اختبرت سميته على الخلايا الطبيعية 68 WRL 0واظهرت النتائج فاعليه المركب كمضاد للاكسدة مقارنة بحامض الاسكوربك كما ظهر في اختبار IC50 بتركيز 53مايكروغرام/مل مقارنة بحامض الاسكوربك بتركيز 28 مايكروغرام/مل0 تبين ان تأثيره السمي على الخلايا الطبيعية لهذا لجرعه خلال الفترة الزمنية 24 و48 و72 ساعة بينما اظهرالمركب تأثير مضاد للورم على الخلايا السرطانيةCAM-1 ,MCF-7 لنفس الفترة الزمنية 24 و48 و72 وهذا التأثير عزز الموت المبرمج للخلايا السرطانية، كما اثر على شكل النواة الطبيعية لخلايا MCF-7بجرعات مختلفة (5، 10، 15) ميكروغرام/مل0حدثت شدة النواة التي ترتبط مباشرة بتغيرات الكروماتين في موت الخلايا المبرمج. لوحظ زيادة نفاذية غشاء الخلايا. أظهرت النتيجة تناقص شدة النواة وزيادة نفاذية الخلية مع زيادة تركيز مركب 2IP المعالج للخلايا.

وقد لوحظ اضطراب في نفاذية غشاء المايتوكوندريا لقدرة هذا المركب على الاخلال بهذه الخاصية والتي اختبرت باستخدام صبغه خاصه بالميتوكوندريا0 ان نفاذية غشاء الميتوكوندريا لخليه MCF-7 المعاملة بمركب 2IPاظهر نتائج انخفاض معنوي ($P<0.05$) انخفاض شده الفلورسنت مقارنه مع الكونترول كما لوحظ تأثره على سايتو كروم سي لخلايا سرطان الثدي المعالجة بالمركب 2IP والتي اظهرت تفعيل اطلاق سايتو كروم سي اعلى من الكونترول بشكل معنوي ($P<0.05$).

نتيجة هذه الدراسة اوضحت اعاقة مركب2IP لمحتويات دنا لخلايا سرطان الثدي نوع MCF-7 لدوره الخلية في اطوار G1 ، G2 ، وM بعد ان تم معاملتها بالمركب 2IP افشل تقدم دوره الخلية في طور G1($P<0.05$) مقارنة مع الكونترول0 اظهرت النتائج فرقا معنويا في تقييد مرحلةG1بطريقة تعتمد على التركيز في خلايا MCF-7.بينما قلت الخلايا في كل من طور G2 وM مع زيادة المعاملة بالمركب0

في الختام ان مركب الاندول المصنع له القدرة على العمل كمضاد اكسدة ومضاد للأورام مما يجعله كعلاج جديد للسرطان.

Chapter One

Introduction

1. Introduction

Cancer is a group of disorders that participate in the uncontrolled joint cell growth that leads to the growth of the cell and that formation called tumorigenesis. The formation of tumor requires the cells to escape the control proliferation and additional growth signal produced, so the cells become resistant to signals that control the growth(Laird, 2005)(Onega *et al*., 2014) and the cell begins to divide in an uncontrolled manner (Cummings & Starr, 2014). The morbidity and mortality of cancer patients increase with the malignant condition in which cancer cells invade the surrounding tissues and distal organs (Anand *et al*., 2008).

One of the most common challenge that the world's face is breast cancer (BC), especially women, as it is one of the most common types of tumors affecting females. BC can be raise from genetic abnormalities with substantial genotypic and phenotypic changes(Bågeman, 2008)(Vaz-Luis *et al*., 2012).In breast, carcinomas start in the cells lining, either the ducts or lobules, but most breast cancers start in ductal cells like that it affects tissues involved in milk production (Ductal and lobular tissues) (C. E. DeSantis *et al*., 2014). However, it is still there are misunderstanding of how that cancer initiate, in addition to spread widely in some countries that suffer from poor health system and diagnosis technology (C. DeSantis *et al*., 2011).

BC is the most tumor among women worldwide, about 25% of all cancers and related to women death(Abood *et al*., 2014). The risk countries to increase mortality are in middle and low income countries. BC was being a main threated to women life in Iraq causing death among female, with mortality rate about 23% (Al Alwan, 2015).

In last ten years in Iraq, there has been a triple increase in the incidence of breast cancer, most of which is due to a particularly aggressive type of cancer (Al-Azzawi, 2006) (Al-Dujaili *et al*., 2008).

The type of treatment was determined dependent on size, stage, degree, if cancer cells have specific receptors, and other characteristics of the tumor; the types of treatment that include surgery, radiotherapy, chemotherapy, and hormone therapy (S. Verma *et al*., 2012).

Chemotherapy means used drugs to destroy cancer cells. Chemotherapy plays a major role in treating patients with gynecological malignancies (Hall *et al*., 2015). In general, chemotherapy has a smaller treatment window compared to other medicines; Consequently, the possibility of severe adverse effects associated with chemotherapy has made patient and drug-appropriate choice critical (Pasquali, 2015).Most chemotherapy treatments are good antioxidants, it play a crucial role in eliminating reactive oxygen species directly or indirectly by preventing the production of these types (Khlebnikov *et al*., 2007).

Some evidence showed that the tumor have a accelerate level of oxidation metabolism than normal cells. This events always are accompanied with high concentration of reactive oxygen species (ROS) production. furthermore, changes in metabolism process related to tumor acceleration (Matés *et al*., 2012). Therefore, cancer cells may be sensitive to medication that generate ROS, or drugs that destroy the ROS scavenging capacity of cells, leading to apoptosis (Reuter *et al*., 2010).

Hence, our dependence on our compound, which is one of the heterocyclic organic compounds, which contains a

heterogeneous atoms such as oxygen, sulfur, or nitrogen in there chemical structure instead of carbon (Alvarez-Builla *et al*., 2011).

Heterocyclic compounds are extensively studied for their applications especially in various bioactivities in medicine and pharmaceutical fields. Heterocyclic compounds have been attracted the attention of many chemists, pharmacists and scientists for their numerous uses in pharmaceutical and medicinal applications (Kaur, 2015)

Schiff bases which preparing from different organic heterocyclic compounds those consisting of indole molecule consider an important class of organic heterocyclic compounds because they have wide range of biological activations including, anti-oxidant, anti-cancer (Ghaidan *et al*., 2018). Anti-bacterial, anti-fungal, anti-inflammatory and anti-viral properties (Rapolu *et al*., 2011) and (Abdulsada *et al*., 2018), antibacterial, antimalarial, anti-proliferative, anti-inflammatory, antiviral and antipyretic properties(Malik & Nema, 2016)(Saif, 2017).

Along medicines history Indole Schiff base derivatives are considered an significant kind of heterocyclic compound which have played important role treating and curing many diseases (Patel *et al*., 2012)and (Sengpracha,2005).

1.2 Aims of the Study is to:

1. Synthesis a new Indole Schiff base, confirmation and characterization the chemical structure of the new synthesized compound.
2. Investigate the antioxidant, acute toxicity and anti-tumor effect(on the MCF-7 Cell Line and CAMA-1**)** of the new Indole Schiff base.