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Pharma, Drug Discovery, Toxicology and Medicine

Male Charles Foster Rats

Paracetamol and Lornoxicam

Highlights

Effects of Blumea Aurita

N-Phenylpiperazine Moiety

Discovering Thoughts, Inventing Future

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Antimicrobial Profile Investigation of Potential Ultrashort Acting *Beta*-Adrenoceptor Blocking Compounds Containing *N*-Phenylpiperazine Moiety

By Ivan Malík, Marián Bukovský, Petr Mokrý & Jozef Csöllei
Faculty of Pharmacy/Comenius University, Slovakia

Abstract - The set of original, highly lipophilic ultrashort acting *beta*-adrenoceptor antagonists containing *N*-phenylpiperazine fragment, labelled as 1–4, was *in vitro* screened for the activity against *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans*, respectively. Following the minimum inhibitory concentration (MIC) assay by the microdilution method, all the tested molecules were practically inactive against both selected Gram-positive and Gram-negative bacterial strains showing the MICs>1.00 $mg \cdot mL^{-1}$. From structural point of view, the presence of ester group and the position of carbamoyloxy moiety within the compounds 1–4 have appeared to be the most notable factors which have decisively influenced the effectiveness against *S. aureus* and *E. coli* compared to the importance of electronic or hydrophobic interactions, which have probably been involved by the presence of *N*-phenylpiperazine, with different membrane components of the bacteria. The current research has also pointed out that the increase in the lipophilicity has been regarded as favourable aspect for the potency of these compounds against *C. albicans*. From entire evaluated set, the molecule 4 has been considered the most active against mentioned yeast with MIC=0.78 $mg \cdot mL^{-1}$.

Keywords : *antibacterial activity, beta-adrenoceptor antagonists, lipophilicity.*

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Antimicrobial Profile Investigation of Potential Ultrashort Acting *Beta*-Adrenoceptor Blocking Compounds Containing *N*-Phenylpiperazine Moiety

Ivan Malík [α], Marián Bukovský [σ], Petr Mokrý [ρ] & Jozef Csöllei [ω]

Abstract - The set of original, highly lipophilic ultrashort acting *beta*-adrenoceptor antagonists containing *N*-phenylpiperazine fragment, labelled as 1–4, was *in vitro* screened for the activity against *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans*, respectively. Following the minimum inhibitory concentration (MIC) assay by the microdilution method, all the tested molecules were practically inactive against both selected Gram-positive and Gram-negative bacterial strains showing the MICs>1.00 mg·mL^{-1}. From structural point of view, the presence of ester group and the position of carbamoyloxy moiety within the compounds 1–4 have appeared to be the most notable factors which have decisively influenced the effectiveness against *S. aureus* and *E. coli* compared to the importance of electronic or hydrophobic interactions, which have probably been involved by the presence of *N*-phenylpiperazine, with different membrane components of the bacteria. The current research has also pointed out that the increase in the lipophilicity has been regarded as favourable aspect for the potency of these compounds against *C. albicans*. From entire evaluated set, the molecule 4 has been considered the most active against mentioned yeast with MIC=0.78 mg·mL^{-1}.

Keywords : antibacterial activity, beta-adrenoceptor antagonists, lipophilicity.

I. Introduction

The term „non-antibiotics“ has been taken to include a variety of the compounds that have been neither antibiotics nor antimicrobial chemotherapeutic agents which have been emloyed in the management of pathological conditions of a non--infectious aetiology, but which have modified cell permeability and have shown broad-spectrum *in vitro* antimicrobial activity [1]. In addition, some of non-antibiotics have been found to enhance the *in vitro* -potency of certain antibiotics against specific bacteria to make them susceptible to previously ineffective substances [2, 3]. An antimicrobial potential of drugs classified as general or local anaesthetics, diuretics, anti-inflammatory compounds, mucolytic agents, proton pump inhibitors, calcium antagonists, antihistamines or psychotherapeutic agents has been already observed and reported in a review [1]. An antimicrobial profile of the antagonists of *beta*-adrenergic receptors, have only been investigated sporadically, and their practical contribution to the management of microbial infections has not been intensively evaluated yet. Despite mentioned, the experimental investigations [4–6] have indicated that some of them have been able to inhibit the microbial growth. Similarly, the surveillance study of Drug Institute in Warsaw [7], which was performed on standard ATCC microbial strains, has revealed the efficiency of matipranolol, therapeutically used as an antiarrhythmic drug and an antiglaucomicum, against *Staphylococcus aureus* as well as certain antihypertensives (i.e. losartan or telmisartan) against *S. aureus* and *Escherichia coli*.

The current article is the continuation of methodical searching and characterising the *in vitro* antimicrobial activity of selected non-antibiotic drugs against mentioned Gram-positive and Gram-negative microbial strains as well as against *Candida albicans*. From structural point of view, the compounds under the study, labelled as **1**–**4**, belong to the class of ultrashort acting *beta*-adrenoceptor blockers due to the presence of the ester bond and connecting 2-hydroxypropane--1,3-diyl fragment as well. As indicated in Table 1, another considerable feature within the structure of inspected molecules is the incorporation of unsubstituted *N*-phenylpiperazine moiety (or, to be more precise, substituted by hydrogen atoms only) which could play an essential role in terms of an antimicrobial efficiency due to possible electronic or hydrophobic interactions with different membrane components of the bacteria [8].

II. Materials and Methods

a) Chemicals and Reagents

The evaluated compounds labelled as **1**–**4** (Table 1), chemically *N*-(2-hydroxy-4-oxa-5-oxy-5-(4-

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-alkoxycarbamoylphenyl)-*N*-phenyl-*N*-piperazinium chlorides, were purchased from Department of Chemical Drugs, Faculty of Pharmacy, University of Veterinary and Pharmaceutical Sciences, Brno, Czech Republic. The estimation of their physicochemical properties, i.e. solubility profile, dissociation constant pK_a, surface activity γ and lipophilicity descriptors (the log k's from RP-HPLC, the R_Ms from RP-TLC), with appropriate readouts has been previously published in the paper [9].

b) The In Vitro Antimicrobial Activity Assay

Microorganisms. An antimicrobial profile of the compounds **1**–**4** was investigated against Gram-positive bacteria *S. aureus* ATCC 6538 (*Micrococcaceae*), Gram-negative bacteria *E. coli* CNCTC 377/79 (*Enterobacteriaceae*) and yeast *C. albicans* CCM 8186 as well. The tested bacterial strains were purchased from American Type Culture Collection (Manassas, United States of America) and Czech National Collection of Type Cultures (Prague, Czech Republic); yeast was obtained from Czech Collection of Microorganisms (Brno, Czech Republic).

Culture media. For a cultivation of the microorganisms, listed in the previous section of this paper, a blood agar, Endo agar and Sabouraud's agar (Imuna, Šarišské Michaľany, Slovak Republic) were used. Blood agar was prepared by adding 10% of defibrine sheep's blood to melted and cooled (50°C) competent components.

Determination of minimum inhibitory concentration (MIC). The MIC values of presently investigated compounds **1**–**4** were carried out by following the procedure previously published in literature [8, 10]. The respective tested molecules have been dissolved in dimethyl sulfoxide (DMSO; Merck, Darmstadt, Germany) due to their very limited solubility in distilled water. Standard suspension of bacteria was prepared from their 24 h cultures which were cultivated on a blood agar (Gram-positive bacteria) and Endo agar (Gram-negative bacteria). Standard suspension of *Candida* was prepared from its 48 h cultures cultivated on Sabouraud's agar.

Prepared suspension contained the concentration of 5×10^7 colony forming unit (CFU) *per* mL of bacteria and 5×10^5 CFU·mL^{-1} of *Candida*, respectively. The UV/VIS spectrophotometry was used for the determination of the microorganisms concentration, all evaluated suspensions were adjusted to the absorbance output of 0.35 at the wavelength of 540 nm.

The suspension of microorganisms was added in the amount of 5 microL into the solutions of inspected compounds (100 microL) and to double concentrated peptone broth medium (8%) for bacteria or to Sabouraud's medium (12%) for *Candida*. The peptone broth and Sabouraud's media were purchased from Imuna (Šarišské Michaľany, Slovak Republic).

Starting concentration of prepared stock solutions was 50.00 mg of respective compound *per* mL of distilled water. These stock solutions (5%) were then serially diluted by a half and final concentrations were 25.00, 12.50, 6.25, 3.13, 1.56, 0.78, 0.39 and 0.20 mg·mL^{-1}, respectively. Antibacterial effect of present DMSO in thus diluted final testing medium was completely lost.

The quantitative screening was performed using sterile 96-well plastic microtiter plates (with round-bottomed wells) with matching covers. Microorganisms were incubated in each well at 37 °C for 24 h. Upon completion of this process, the volume of 5 microL of evaluated suspension has been taken from each well by using transferring tool and cultured on a blood agar (*S. aureus* ATCC 6538), Endo agar (*E. coli* CNCTC 377/79) or on Sabouraud's agar (*C. albicans* CCM 8186), respectively. Petri dishes were then incubated for 24 h at 37 °C.

Positive control using only an inoculation of the microorganisms and negative control using only DMSO were realized parallelly. Both DMSO and nutrient concentrations remained stable in each well, only the concentration of inhibitory compound has changed. All experiments were performed in duplicate. The MIC was regarded as the lowest concentration of antimicrobial agent required to inhibit the visible growth of microorganism after incubation [11]. The MIC was dependent on the presence/absence of the culture on used solid media after the transfer of 5 microL of suspension from each well. The values of MIC which have been estimated for tested compounds as well as for DMSO (due to comparison) are reported in Table 1 in mg·mL^{-1} units.

III. Results and Discussion

Possible structural and physicochemical aspects of *beta*-adrenergic receptors antagonists under the study (Table 1) which could substantially affect their antimicrobial properties were: (i) the position of carbamoyloxy (NHCOO) group which has not been inserted between 2-hydroxypropane-1,3-diyl connecting chain and the aromate; (ii) the presence of carboxy (COO) group directly attached to lipophilic aromatic ring; (iii) possible electronic and hydrophobic effects which have been induced by the substituent forming basic part of the molecule; (iv) the lipohydrophilic properties.

Following the quantification of an antibacterial efficiency which has already been published in a paper [12], the entire set of currently inspected compounds **1**–**4** has been regarded as completely inactive against both tested bacterial strains showing the MICs in the range of 6.25–25.00 mg·mL^{-1} for *S. aureus* and 6.25–12.50 mg·mL^{-1} for *E. coli*, respectively (Table 1). Previously performed experiments [8] have pointed out that the incorporation

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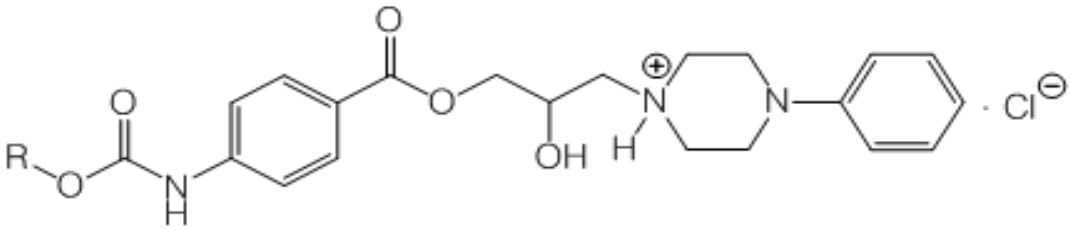
of polar carbamoyloxy group between lipophilic aromatic ring and 2-hydroxypropane-1,3-diyl connecting chain has been considered very essential for the activity maintenance. On the contrary, the absence of direct covalent bond between carbamoyloxy moiety and given connecting string has led to the loss of the potency, as current experimental results have indicated. Identical conclusions have been also reported in previously published article of Malík et al. [10].

Furthermore, current experimental data could lead to the assumption that ester bond within the structure of tested componds **1**–**4** would be splitted due to the enzymatic equipment of both tested bacterial strains. Possible electronic or hydrophobic interactions, induced by integrated *N*-phenylpiperazine moiety, with certain membrane elements of the bacteria have been previously considered important [8] but the presence of direct bond between polar carbamoyloxy moiety and connecting chain has seemed to be more significant factor in terms of the activity against *S. aureus* and *E. coli* as well. It could be suggested that possible isosteric replacement of carboxy moiety for etheric bridge (the bond which would probably be more resistant to enzymatic splitting) could improve an antibacterial profile of such designed compounds.

All evaluated structures **1**–**4** have been regarded as highly lipophilic because of bearing two aromatic rings and hydrocarbon chain as well. Their lipophilicity enhancement due to alkyl substituent elongation has meant the decrease in the MIC values for *S. aureus*. However, as indicated in Table 1, no MIC entry has been lower than 1.00 mg·mL^{-1}.



Entry	*R*	MIC (mg·mL^{-1})		
		S. aureus	*E. coli*	*C. albicans*
1	CH_3	25.00	6.25	3.13
2	C_2H_5	25.00	12.50	3.13
3	C_3H_7	12.50	6.25	1.56
4	C_4H_9	6.25	6.25	0.78
DMSO	–	25.00	25.00	6.25

Table 1 : The *in vitro* antimicrobial activity of investigated structures **1**–**4** against selected microbial strains

It has been already reported that the parameters characterising the lipophilicity have been linearly related to the inhibitory activity against *C. albicans* for structurally similar set of the compounds bearing *meta*-alkoxyphenylcarbamoyloxy fragment directly bonded to 2-hydroxypropane-1,3-diyl connecting chain [8]. Additionally, the presence of highly lipophilic, sterically bulky substituent, which has shown primarily electron-withdrawing effect, attached to *N*-phenylpiperazine (trifluoromethyl group into *meta*--position) has been considered favourable, leading to more effective molecules with their MIC outputs in the interval of 0.10–0.20 mg·mL^{-1}. Following current experimental readouts, the increase in the lipophilicity of tested series **1**–**4** has meant a slight increase in the activity against mentioned yeast. The maximum of the effectiveness has been noted for the compound **4**, as indicated in Table 1 (MIC=0.78 mg·mL^{-1}). Furthermore, it could be assumed that eventual incorporation of i.e. trifluoromethyl substituent into *meta*-position of *N*--phenylpiperazine fragment within the structure of investigated set **1**–**4** would even lead to more active compounds against *C. albicans*.

IV. Conclusion

The results of current study have pointed out that the presence of polar ester group directly attached to 2-hydroxypropane-1,3-diyl moiety, which has been integrated within the structure of evaluated prospective *beta*-adrenergic receptor blockers, has propably been responsible for the complete loss of their activity against both tested bacterial strains, *S. aureus* and *E. coli*. Furthermore, assuming the position maintenance of ester (carboxy) moiety within currently inspected compounds, the nature of basic fragment, (substituted) *N*-phenylpiperazin-1-yl, and consequent electronic and hydrophobic interactions with specific components of bacterial membrane as well as the increase in the lipophilicity could be regarded as very substantial but probably not decisive factors which have positively

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influenced the activity of such molecules against aforementioned tested microorganisms. On the contrary, relatively highly lipophilic antagonists of *beta*--adrenergic receptors would be promising in terms of their efficiency against *C. albicans*.

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Assessment of Substance Abuse and Associated Factors among Students of Debre Markos Poly Technique College in Debre Markos Town, East Gojjam Zone, Amhara Regional State, Ethiopia, 2013

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Methods: A cross sectional study was conducted to determine the overall prevalence of substance abuse among students and factors associated with it. Simple random sampling technique was conducted to select 423 students from the list of students name in their respective batch after stratifying them based on year of study. A pre-tested semi structured anonymous questionnaire was used to collect data, which was entered and cleaned using Epi Data version 3.1 and analyzed using SPSS version 16.0 statistical package. Descriptive statistics and logistic regression were performed to examine the prevalence and predictors of substance abuse. CAGE-AID was used to measure substance abuse.

Results: The overall prevalence of substance abuse was 14.1 %. The commonly abused substances were alcohol 13.4 %, khat 7.8 %, and cigarette 5.4 %. Sex [AOR, 95% CI; 3.550 (1.451, 8.685)], peer pressure [AOR, 95% CI 3.405 (1.047, 11.076)], availability of the drugs [AOR, 95% CI 3.394 (1.677, 6.868)],family drug use[AOR, 95% CI; 2.698 (1.337, 5.443)], personal pleasure [AOR, 95% CI 3.346 (1.315, 8.512] and academic dissatisfaction [AOR, 95% CI 2.739(1.253, 5.985)] were found to be significantly associated with students to abuse substances.

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Assessment of Substance Abuse and Associated Factors among Students of Debre Markos Poly Technique College in Debre Markos Town, East Gojjam Zone, Amhara Regional State, Ethiopia, 2013

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Conclusion and Recommendation: A significant proportion of students abuse substances. Teachers in the high schools and colleges, parents, mass media and other concerned people should teach students about the health and social problems associated with substance abuse.

I. Background

History of Substance /drug abuse is as old as history of mankind. Human beings have been using the different parts of plants as medicine for reliving different health conditions. The extent of illicit drug use is mainly seen among the youth [1].

Substance abuse is Persistent or sporadic drug use inconsistent with or unrelated to acceptable medical practice. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following: failure to full fill major role obligations at home, school or work; substance use in situations in which it is physically hazardous; recurrent substance-related legal problems; continued substance use despite having persistent or recurrent social or interpersonal problems exacerbated by the effects of the substances [2].

Substance abuse is becoming a serious ongoing public health problem; it affects almost every community and family in some way. Globally, there were about 190 million substance abusers. Out of these substance abusers, around 40 million serious illnesses or injuries were identified each year. The trend is increasing as period goes [3]. Use of substances such as alcohol, *khat* leaves (*Catha edulis*) and tobacco has become one of the rising major public health and socio-economic problems worldwide. Recent trends indicate that the use of substances have dramatically increased particularly in developing countries. Alcohol, especially in high doses, or when combined with *khat* or tobacco, continues to claim the lives of many people. It is estimated that 9% of the global population aged 12 or older are classified with dependence on psychoactive substances such as alcohol [4].

The history of psychoactive substance use in Africa is relatively short except for the reports on the use of traditional substances such as alcohol, cannabis and khat. The introduction of prescription drugs to Africa drastically increased the availability and use of psychoactive substances. This notwithstanding, alcohol, cannabis and khat still remain the most common substances of abuse in Africa [5].

Existing literature on alcohol consumption among adolescents in sub-Saharan Africa suggests that a substantial proportion of adolescents have consumed

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or currently consume alcohol. Two Ghanaian studies conducted among secondary school students and among nationally- representative samples of in- and out-of-school youth found that the prevalence of lifetime alcohol use was approximately 25% [6].

Substance misuse is a growing problem in Ethiopia, as in many developing countries. Alcohol and khat are the most frequent substances of abuse, followed by cannabis and solvents. Hard drugs such as heroin and cocaine are rarely used [7]. Studies on substance abuse in selected urban areas showed that 82 % of street children, commercial sex workers, and street vendors as having used addictive drugs or substances. They also reported that Khat, alcohol, hashish, tobacco, and solvents were the most abused substances. Heroin, cocaine, and other narcotic drugs were not considered to be important [8].

Some studies have indicated that substance misuse is associated with psychological distress, suicide attempts functional impairment, physical ill-health and risk taking behavior. Khat (an evergreen plant with amphetamine-like properties) and alcohol are among those substances widely consumed among the youth of Ethiopia. In a study of over 10,000 adults in Butajira, a higher prevalence of mental distress and suicide attempt was found in those using alcohol and khat [9]. An increased prevalence of suicide attempts was also reported in adolescents in Addis Ababa who drank alcohol [10]. Khat use has been associated with physical illness, injuries, under nutrition, mental distress, sleep disorders, problem drinking and heavy smoking [11], as well as recurrent brief psychotic episodes with associated violent behavior [12]. In a case-control study, khat use has also been found to be a risk factor for HIV infection [13].

A study conducted in Amhara region, among college students of North Western Ethiopia revealed that, the prevalence of cigarette smoking seemed to decrease among university students but the decrease in the prevalence of khat chewing is not remarkable. Lung diseases including lung cancer were mentioned as health risk of cigarette smoking [14]. In a cross sectional study, alcohol intake and chewing of chat were factors predisposing out-of-school youths to HIV/AIDS-related risky sexual behavior [15]. According to a baseline assessment for HIV counseling and testing program in Amhara region, substance abuse (of chat, hashish, and shish a) is very common in most of the towns, contributing to the spread of sexually transmitted infections / HIV. Chat chewing houses are everywhere and attract all segments of the population, especially the youth [16].

A baseline survey in East gojjam zone revealed that, substance abuse such as high alcohol drinking, khat and shisha were the push factors for early sex initiation to adolescents and youths. In-school girls' sexual networks extend from school boyfriend to older men, especially drivers and civil servants [17].

Debre Markos town is characterized by a significant number of people whose livelihood depends on the informal sector, such as petty traders, day laborers, and local brew sellers. The newly built college and technical schools have increased the number of youth coming to Debre Markos town. This led to cultural change among youth, including early sexual debuts and premarital sex. Some of the college girls who live in rented houses practice sex with married and single men in return for money. Male civil servants are said to have sexual networks with college girls. The other important risk is FSWs and their sexual networks with married men and in-and-out-of-school youth [16].

Substance use and HIV/AIDS are interrelated due to the effect of drugs on human behavior [18]. Debre Markos is best known producing Ethiopian homemade beer Tella, homemade liquor Arekie and the famous Honey Wine or Teji. Students visit local beverage houses, chat bets, and other drug abuse sites, it leads to the spread of HIV AIDS. A study conducted in Debre Markos town revealed that selling local beverages like Arakie, Teji and Tella was positively associated with the spread of HIV AIDS [19].

The rationale behind this study is that, there is little data concerning commonly abused psychoactive substances in Debre Markos Town though substance abuse is an emerging public health problem. And also, as far as my knowledge and searching effort, no study was conducted on substance abuse among students of Debre Markos Polytechnic College. The problem is usually overlooked. So, this study is designed to bridge the fore mentioned gaps.

II. Methods

The study was conducted in Debre Markos polytechnic college in Debre Markos Town, the capital city of East Gojjam Zone. Before one and half centuries ago, Tedla Gualu governed Gojjam. During this time, or to be more precise, in 1853 Dejazmach Tedla found Menkorer, presently known by Debre Markos. In 1881 the first Church-Saint Markos was introduced in Menkorer. Just a year after and onwards, the town got a name Debre Markos after the church of St Markos [27].

Debre Markos is found 300 kilometers Northwest of Addis Ababa and 265 kilometers Southeast of the Amhara National Regional State capital city-Bahir Dar. The geographical coordinates of the town are10°20′ latitude north and 37°43′ longitude east. The town is situated at 2420 meters above sea level, the weather condition, in most of the time is, 'Woinadega' [28].

Based on the 2007 Census conducted by the Central Statistical Agency of Ethiopia, this town has a total population of 62,497, of whom 29,921 are men and 32,576 women. The three largest ethnic groups reported in the town were Amhara (97.12%), Tigrinya (1.29%), and Oromo (0.67%); all other ethnic groups made up 0.92% of the population. The majority of the inhabitants

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practiced Ethiopian Orthodox Christianity, with 97.03%, while 1.7% of the populations were Muslim and 1.1% was Protestants [29].

There is one Polytechnic college in the town which is established in 1982. The total number of students enrolled in this college for the academic year 2012/2013 both in regular and night program are above 3050.

The study was conducted on March 27, 2013 among students of Debre Markos Poly Technique College in Debre Markos Town using Institutional based cross-sectional study design.

The source population was all students of Debre Markos polytechnic college in Debre Markos Town during the specified study period and the study population was only regular students of Debre Markos polytechnic college in Debre Markos Town during the specified study period.

The sample size was calculated by using the formula for single population proportion for cross sectional survey and taking the proportion as 50%, (since no study was conducted in the study area as far as the investigator knowledge and searching effort) with confidence level of 95% and degree of precision of 5%. An additional 10 % was added to the sample size as a contingency for non responses. The calculated sample size was 384 and adding a 10% of non- response rate, the total sample size was 423.

First students were stratified based on year of study. Then, simple random sampling technique was applied to select individuals in each year of study from the list of students name in their respective batch. Students from each year of study were selected proportionally to their population size.

Data was collected by semi structured self-administered questionnaire prepared in English and translated to Amharic and retranslated to English to ensure its consistency. The questionnaire was adopted and modified from WHO-students drug use survey questionnaire. Pretest was conducted in 5% of the sample size in Amanuel TVET College a nearby town and necessary corrections to the tool were made before the use of the questionnaire in the actual survey/site. Data collectors were contacted through student counselors of the college; they agreed on administering the survey in the same day and time to prevent contamination of information. Participation was on voluntary basis and confidentiality was maintained to encourage accurate and honest self-disclosure. After that, the questionnaire was distributed to the selected students in the classroom and when the instructors are willing to allow the students to complete the questionnaire, the filled questionnaires were collected immediately.

III. Inclusion and Exclusion Criteria

Regular students of Debre Markos polytechnic college who are willing to participate in the study during the time of data collection were included and students who are critically sick (to the extent of unable to read and write) and those who are out of the campus for practical attachment during the time of data collection were excluded.

IV. Operational Definitions

CAGE-AID: is derived from the four questions of the tool: Cut down, Annoyed, Guilty, and Eye-opener; it helps to determine if substance abuse exists [26].

Current use: having consumed any abused substance at least once in the past 30 days.

Ever use: an individual is considered as ever consumed even if he/she will consume only once in his/her lifetime.

"Hard" drugs: Substances such as cocaine, heroin, etc, which are under the International control and produced, trafficked and consumed illicitly [1].

Illicit drugs: A psychoactive substance, the production, sale or use of which is prohibited [26].

Life time use:-The proportion of students who had ever consumed any of abused substance [26].

Substance: For this study it was defined as alcohol, khat, cigarettes and illicit drugs to alter their mood or behavior.

Substance abuse: For this study it was defined as the abuse of alcohol, khat, cigarettes and illicit substances by college students and fulfills the criterion (CAGE ≥2).

In order to assure data quality, high emphasis was given to minimize errors using the following strategies: the questionnaire was pretested and subsequent correction and modification has been done; the data collectors and the supervisors were trained on the data collection technique for one day. The collected data was reviewed and checked for completeness before data entry.

Data was entered into Epi Data version 3.1 for data exploration and cleaning. The cleaned data was exported to SPSS version 16.0 statistical packages for statistical analysis. The prevalence of substance abuse was determined by taking frequencies and percentages. Bivariate associations between dependent and several independent variables were examined. Multivariate logistic regression analysis was employed to identify factors associated with substance abuse by controlling for the effects of potential confounding variables. Odds ratio was calculated to determine the strength of associations between selected variables.

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V. Measurement used to Measure Substances Abuse

a) *CAGE-AID: CAGE Questions Adapted to Include Drug Use*

1. Have you ever felt you should cut down on your drinking or drug use?

2. Have people annoyed you by criticizing your drinking or drug use?

3. Have you felt bad or guilty about your drinking or drug use?

4. Have you ever had a drink or used drugs first thing in the morning to steady

Your nerves or to get rid of a hangover (eye-opener)?

Scoring: Item responses on the CAGE questions are scored 0 for "no" and 1 for "yes" answers.

A total score of two or greater positive answers of the above four questions is considered as fulfill the criteria of substances abused [26].

VI. Ethical Considerations

Initially ethical clearance was obtained from Debre Markos University Institutional Research Ethics Review Committee. Then, permission was obtained from the dean of Debre Markos Poly Technic College before data collection. All selected students were communicated about the study in order to obtain their verbal consent before administering questionnaires. To ensure convenience of teaching process some academic and administrative staffs were communicated about the study. Participants were informed that they have full right to discontinue or refuse to participate in the study. The data collectors informed participants about the absence of harm as a result of their participation. After gaining their willingness the data was collected by administering the questionnaire.

VII. Results

Socio-demographic Characteristics of Study Participants a total of 423 questionnaires were distributed, of which 410 were filled consistently and completely with response rate of 97%. Two hundred twenty five (54.9%) of the samples were males. The mean age of the participants was 19.8 ± 2.1 years.

The majority of respondents 398 (97.1%) were Amhara. Out of the total respondents, 393 (95.9%) were Orthodox followers. From the total participants, 242 (59%) were first year students. The previous place of residence for the majority of respondents, 251 (61.2 %) were from urban setting. The prominent family occupation was merchant which was 42.4 % followed by farmer 26.3%. About family's educational status, fathers of 9.0 % and mothers of 30.2 % of the respondents cannot read and write. Whereas fathers of 51.2 % and mothers of 40.2 % of the respondents were can read and write. 23.2% of respondents' family uses substances/drugs and 76.8 % were non users.

Table 1 : Socio-demographic characteristics of Debre Markos Poly Technic College students (n=410), Amhara, Ethiopia, March 27, 2013

Variables	Frequency (n=410)	Percentage (%)
Sex		
Male	225	54.9
Female	185	45.1
Age group		
15-19	210	51.2
20-24	186	45.4
25-29	14	3.4
Ethnicity		
Amhara	398	97.1
Tigray	7	1.7
Oromo	4	1
Gurage	1	0.2
Religion		
Orthodox	393	95.9
Muslim	8	2
Protestant	7	1.7
Catholic	2	0.5
Study year		
Year I	242	59
Year II	144	5.1
Year III	24	9
Residence (before joining college)		
Urban	251	61.2
Rural	159	38.8
Family occupation		
Farmer	174	26.3
Merchant	108	42.4
Gov't employee	66	16.1
Ngo employee	18	4.4
Housewife	27	6.6
Daily laborer	5	1.2
Private employee	10	2.4
Others*	2	0.5
Father's Educational status		
Cannot read and write	37	9.0
Can read and write	210	51.2
Primary (1-8 grades)	43	10.5
Secondary (9-12 grades)	37	9.0
Tertiary (above 12 grades)	81	19.8
Others*	2	0.5
Mother's Educational status		
Cannot read and write	124	30.2
Can read and write	165	40.2
Primary (1-8 grades)	49	12.0
Secondary (9-12 grades)	31	7.6
Tertiary (above 12 grades)	39	9.5
Others*	2	0.5
Family use of substance /Drug		
Yes	95	23.2
No	315	76.8

N.B: *= No family

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a) *Magnitude of Substance use among Students of Debre Markos*

i. *Poly Technique College*

Out of the total subjects, 61.7% of the respondents were reported ever using at least one substance in their lifetime. Nearly 38% were current users of any substances. 35.4% were current alcohol consumers. 6.3% of study participants were chewed khat 30 days prior to data collection. 4.4% and 1.7% were smoked cigarettes and used illicit drugs respectively.

Table 2 : Prevalence of Substance Users among Debre Markos Poly Technic College students (n=410), Amhara, Ethiopia, March 27, 2013

Variables	Ever Users		Current Users	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
Any substance				
Yes	**253**	**61.7**	**157**	**38.3**
No	**157**	**38.3**	**253**	**61.7**
Alcohol				
Yes	246	60	145	35.4
No	164	40	265	64.6
Khat				
Yes	55	13.4	26	6.3
No	355	86.5	384	93.7
Cigarettes				
Yes	32	7.8	18	4.4
No	378	92.2	392	95.6
Illegal drugs				
Yes	11	2.7	7	1.7
No	399	97.3	403	98.3

b) *Current users of specific substances among the ever users*

Nearly 64 % of ever users of illicit drugs were current users; 59% of ever drunker were currently drunk alcohol; approximately 56% of ever smokers were persisting to smoke currently and comparably, 47% ever khat users were currently chewed khat.

Table 3 : Current specific substance users among ever users of Debre Markos Poly Technic College students, Amhara, Ethiopia, March 27, 2013

Variables	Frequency (n)	Percentage (%)
Khat (n=55)		
Yes	26	47.3
No	29	52.7
Cigarettes (n=32)		
Yes	18	56.3
No	14	43.7
Alcohol (n=246)		
Yes	145	59
No	101	41
Illegal drugs (n=11)		
Yes	7	63.6
No	4	36.4

c) *Percentage distribution of substance use by sex*

Comparing to females, male respondents account for almost 67% and 75 % ever and current users of any substances respectively. From currently users males account 73.8 % for alcohol drinking, 88.5 % for khat chewing, 77.8 % for cigarette smoking, and 100 % for illicit drug use respectively.

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Table 4 : Percentage distribution of substance use among Debre Markos Poly Technic College students by sex, Amhara, Ethiopia, March 27, 2013

Variables	Ever Users		Current Users	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
Any substance				
Male	169	66.8	118	75.2
Female	84	33.2	39	24.8
Alcohol				
Male	163	66.3	107	73.8
Female	83	33.7	38	26.2
Khat				
Male	47	85.5	23	88.5
Female	8	14.5	3	11.5
Cigarettes				
Male	25	78.1	14	77.8
Female	7	21.9	4	22.2
Illicit drugs				
Male	10	90.9	7	100
Female	1	9.1		

d) The time in which students started to use abused substances

Concerning initiation time of substance use, 36 % of participants started to use abused substances when they were elementary school students. 35.6% of the respondents started during secondary school life. 15.4 % and nearly 11 % of the respondents had started when they were at preparatory school and college life respectively.

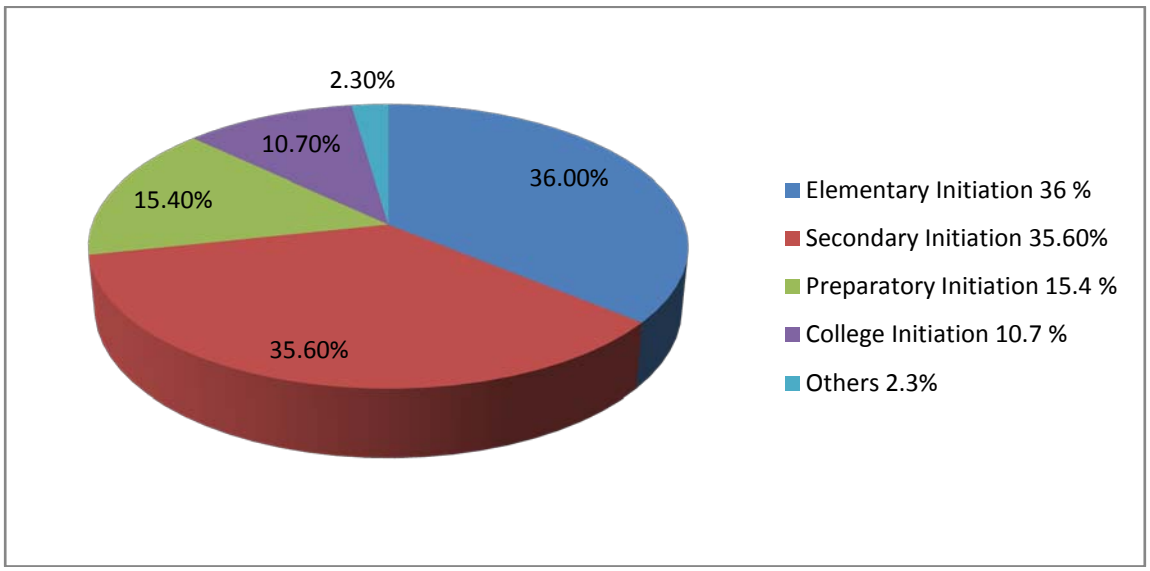

Figure 1 : Time of Initiation to Use Abused Substances among Debre Markos Poly Technic College students (n=253), Amhara, Ethiopia, March 27, 2013

e) Reasons to start abused substances

Different reasons were mentioned by students for the use of drugs. The prominent reasons for starting to use substances among the ever users were due to peer pressure 56.7 %, to get personal pleasure 48 %, due to availability of substances 36.8 %, due to academic dissatisfaction 27.5 %, to stay awoke 22.1 % and the least was to get relief from tension 15 %.

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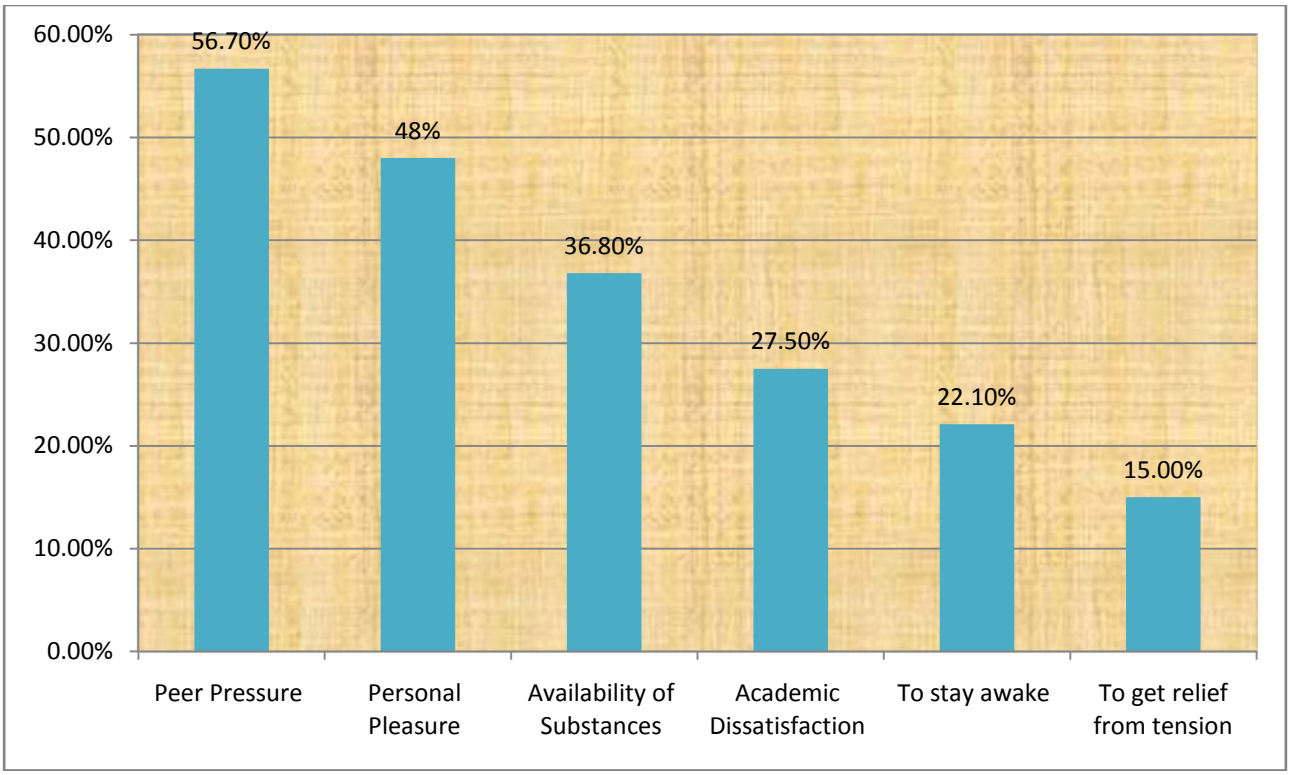

Figure 2 : Reasons to start substances to use among Debre Markos Poly Technic College students (n=253), Amhara, Ethiopia, March 27, 2013

f) Magnitude of Substance Abuse among Debre Markos Poly Technique College Students

Fifty eight (14.1 %) respondents fulfilled the criteria of substances abuse (CAGE ≥2). Fifty five students (13.4 %) were alcohol abusers followed by khat thirty two (7.8 %) and cigarette twenty two (5.4 %). Eight respondents (1.95 %) abuse illegal drugs. Alcohol, Khat and cigarette were the commonest abused drugs. The nature of substances abused includes both legal and illegal substances.

Table 5 : Prevalence of Substance Abuse among Debre Markos Poly Technic College students (n=410), Amhara, Ethiopia, March 27, 2013

Variables	Frequency(n)	Percentage
Substance abuse		
Yes	58	14.1
No	352	85.9
Khat abusers		
Yes	32	7.8
No	378	92.2
Cigarettes abusers		
Yes	22	5.4
No	388	94.6
Alcohol abusers		
Yes	55	13.4
No	356	86.8
Illicit Substance abusers		
Yes	8	1.95
No	402	98.05

g) Associated Factors for Substances Abuse

Against substances abuse, variables such as socio demographic characteristics, initiation time of substance use, and reasons to start were determined using logistic regression model. Variables which are significantly associated in the first model (p ≤0.2) were taken and analyzed together by multivariate logistic regression. Confounding factors were adjusted by multiple logistic regression analysis. After controlling for the effects of potentially confounding variables using multivariate logistic regression, socio demographic characteristics, peer pressure, drug availability,

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academic dissatisfaction, and seeking for personal pleasure were found to be significantly associated with substance abuse. Variable to get relief from tension have significant association with students to abuse substances in the bivariate analysis disappear in the multivariate analysis. Factors which are significantly associated with substance abuse in the multivariate analysis were elaborated in the following paragraph.

Substances abuse in males was three and half times higher than in female respondents: [AOR, 95% CI; 3.550 (1.451, 8.685)], students coming from urban areas were more likely to abuse substances than those who were coming from rural areas with [AOR, 95% CI; 3.342 (1.532, 7.288)]. Students whose families use substances were 2.7 times more likely to abuse substances as compared to those who did not: [AOR, 95% CI; 2.698 (1.337, 5.443)]. Respondents who started to use substance through peer pressure [AOR, 95% CI 3.405 (1.047, 11.076)] were 3.4 times more likely to abuse substances as compared to those who did not. Subjects who began to use substances because of availability of the drugs [AOR, 95% CI 3.394 (1.677, 6.868)] were 3.4 times higher as compared to those who did not. Similarly respondents who started to use substances for personal pleasure [AOR, 95% CI 3.346 (1.315, 8.512)] and due to academic dissatisfaction [AOR, 95% CI 2.739(1.253, 5.985)] were 3.3 times and 2.7 times higher respectively as compared to those who did not. (See table 7).

Table 6 : Association of factors towards substances abuse among Debre Markos Poly Technic College students (n=410), Amhara, Ethiopia, March 27, 2013

Variables			Substances abuse		OR(95%)CI
	Yes	No	Crude	Adjusted	P-Value
Sex					
Male	49	176	3.403(1.580, 7.328)*	3.550(1.451, 8.685)*	0.006
Female [1]	9	176	1	1	
Residence					
Urban	45	206	2.675(1.357, 5.274)*	3.342(1.532, 7.288)*	0.002
Rural [1]	13	146	1	1	
Family drug use					
Yes	31	64	3.076(1.680, 5.632)*	2.698(1.337, 5.443)*	0.006
No[1]	27	288	1.	1	
Reasons to start					
Peer pressures					
Yes	54	144	4.781(1.649, 13.865)*	3.405(1.047, 11.076)*	0.042
No[1]	4	51	1	1	
Availability of drugs					
Yes	36	57	3.962(2.145, 7.318)*	3.394(1.677, 6.868)*	0.001
No[1]	22	138	1	1	
Personal pleasure					
Yes	51	127	3.901(1.679, 9.064)*	3.346(1.315, 8.512)*	0.011
No[1]	7	68	1	1	
Academic dissatisfaction					
Yes	20	32	2.681(1.384, 5.192)*	2.739(1.253, 5.985)*	0.012
No[1]	38	163	1	1	
To get relief from tension					
Yes	34	76	2.218(1.222, 4.028)*	1.299(0.631, 2.675)	0.478
No[1]	24	119	1	1	

N.B: *= Statistically significant at P<0.05,
[1]= Referent factors

VIII. Discussion

In this study a significant proportion (14.1%) of students were abused substances. This prevalence was lower than the report from students of Mekelle University 20.1 % [26] and the national findings obtained from National Survey on Drug Use and Health, 20.2% [30]. And it is remarkably lower than the report from undergraduate students in public Midwestern University, 48.1 % [31]. This difference may be due to the difference in population under study and area. For Mekelle University students, more than sixty five percent of study participants were males and according to our finding male sex was positively associated with substance abuse. Or, the difference might be due to method difference (measurement of substances abuse).

The findings of this study revealed that the commonly abused drugs were alcohol 13.4%, khat 7.8%, cigarette 5.4% and other illicit substances (1.95%). Apart the prevalence, this is in agreement with findings in students of Mekelle University, alcohol 16.6%, khat 14.8%, and cigarette and cannabis 8.8% was

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abused equally [26], in secondary school of Kenya in 2009 alcohol 42.9%, khat 20.8%, cigarette 19.8% and cannabis 14.3%, were commonly abused substances [32]. Again studies in various parts of the country have noted that alcohol was the most commonly used psychoactive substance, which was similar with the result of this study [20, 33]. As compared to other drugs high spread of alcohol, khat and cigarette abuse may be due to social, cultural and legal acceptability. In addition to this, these drugs were internationally uncontrolled or Social Substances of Abuse might be also another reason. Specifically for alcohol might be, alcohol unlike other drugs does not have a drastic effect on personal health when consumed moderately; it is readily available and it is consumed mainly in pubs and other entertainment centers which could attract youths; and more accepted in the society compared to other types of drugs. Most alcohol commercials have very attractive scenes. The people in the advertisements are very happy and enjoying their drinks. As a result, students take alcohol to experience what they have already seen on television [20].

The present findings show that, being male; coming from urban areas and parental use of substances were strongly and positively associated with students to abuse substances. This is in agreement with study conducted among Addis Ababa high school students; there is statistical significant association between family use of substances /drugs with students to abuse substances /drugs [1]. Previous studies also identified that friends' and parental use of substances were strongly associated with the use of substances among adolescents, indicating the influence of peer pressure [34, 35, 36]. This influence of the behavior of families and friends suggests that interventions should be multi directional involving different sections of the population at the same time.

Students who started to use substance due to peer pressure, readily availability of substances, seeking for personal pleasure and academic dissatisfaction were positively associated with students to abuse substances. This is in agreement with studies conducted in Kenyan Secondary Schools [20]. Consistent to this, peer pressure and readily availability of substances were positively associated with students to abuse substances in Mekelle University [26].

In this study, the prevalence of ever users of substances was found to be 61.7%. This is lower than findings reported in Mekelle University students, 82.7% [26], Nigerian medical university, 78% [37], western Kenya, 69.8% [32] and Nigerian secondary school, 63.3% [33]. This difference might have occurred due to cultural and regulation difference of the substance use among the countries. The time the research was undertaken could be another reason for the variations.

The present survey reported that 36 % of the ever users began at elementary school. Which is different from reports taken from students of Mekelle University 30.80 % at secondary level [26] and from National Survey on Drug Use and Health (users started at 19 years at which students joined higher education in our context) [30]. A Finding from college students of North West Ethiopia was different, 52% at university level for khat and 46% at preparatory level for cigarette [14].

The study further revealed that 56.7 % the study subjects were introduced to use substances by a friend/peer. This is consistent with the study done among students of Mekelle University 58.8 % [26] and much lower than the study conducted in Nigeria, 75.1 % [37]. Another study in Kenya secondary school revealed that readily available drug and peer group pressure were the prominent reasons to begin substances use [20].

The proportion of ever alcohol drinkers of this study were 60 %. The finding of this study is lower than the study among students of Mekelle University, 69.7%,[26], findings reported from students of Ambrose Alli University; Ekpoma, Nigeria representing 66% [38] and in line with 61% among Chinese, University Students in Hong Kong [39]. But it is slightly higher than reports from private high school students in Addis Ababa 57.7% [40]. The difference in educational program between countries could be contributing factors for this varying rate of alcohol consumption.

In addition, based on this study, 13.4% of the participants were ever khat chewers. This finding is lower than the study in Addis Ababa, 35.6% [40], the study conducted among College students in North Western Ethiopia 26.7 % [14] and much lower than the study in high school students in south-western Ethiopia, 64.9% [21]. Current khat chewers in this study were 6.3% of the study subjects. This is lower than a report from Jazan region of Saudi Arabia in which the prevalence of khat use among high school students was 21.4% [41], the study conducted among college students of North West Ethiopia 17.5% [14], the study done among Haramaya University students 20.3 % [25], the study among Jimma University staffs which was 30.8% [24]. The possible explanations for the observed differences in khat chewing could be due to differences in sample characteristics, in the definitions used by studies, cultural differences in understanding of the amount of chewing and methodological differences.

The prevalence rate of lifetime cigarette use in this study was 7.8%, which is lower than the study conducted among College students in North Western Ethiopia 13.1 % [14], study done among Mekelle University students 17.5 % [26], findings from Secondary School of Nigeria 14.3% [33], report from Chinese University, 13% [31]. In contrast, it is higher than findings obtained from Western Kenya, 2% [32]. The discrepancy could be due to the population's prevailing social, cultural variations and study time difference in the respective countries.

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Even though illicit drugs such as cannabis, ganja / shisha, heroin and marijuana were legally prohibited, this study revealed that ever users of cannabis was 0.7%, ganja / shisha 2.2 %, and heroin and marijuana 0.2 %, were used equally. This is lower than reports from Addis Ababa high school students, which was 1.1 %, 3.3 %, 0.4 %, 0.7 % for cannabis, ganja / shisha, heroin and marijuana respectively [1]. This might be due to differences in area, population under study as well as the time the research was undertaken.

In general, the difference indicated in the above discussion might be due to the population difference under study, and promotion of publicity. The difference in educational program between countries and the time the research was undertaken could also be contributing factors for this varying rate of substance use and abuse. Organizational, physical and behavioral property variables of campuses, including the type of residence, institutional size, location and campus community property variables could also be reasons to the variations.

IX. Conclusion and Recommendation

The present study aimed at assessing the magnitude of students' substance abuse and associated factors. Accordingly, it has come up with the following conclusions.

A significant proportion of students abuse substances. It was associated positively with certain variables such as male participants, urban setting, family drug/substance use, peer pressure, availability of drugs, personal pleasure and academic dissatisfaction. The commonly abused substances were alcohol, khat, and cigarette. Therefore, actions targeting on those predictors are necessary to effectively reduce substance abuse among college students.

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Effect of Oral Administration of Chloramphenicol on Hematological Profile of Male Charles Foster Rats

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Abstract - For a given organism, relevant information about the internal environment can be easily accessed by its hematological profile. Chloramphenicol being a potent broad spectrum antibiotic is used readily in eyed drop formulations and is also in food industry. In the present study, varying doses (750, 1500 and 2250 mg/kg B.Wt) of Chloramphenicol (CAP) was administered orally as single daily dosage for 24 days to Male Charles Foster rats, to assess the hematological changes associated with oral exposure to the drug. The results showed a significant ($p<0.05$) dose dependent decrease in Red Blood Cells (RBC) count, Hemoglobin (Hgb), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin Concentration (MCHC) and increase in Hematocrit (Hct), White Blood Cells (WBC) and Platelets compared to the initial blood profile. The results recorded in this present study suggested that exposure to CAP results in Hematotoxicity. Hence, the potential of CAP to cause hematotoxicity is reported in the study.

Keywords : *CAP, hematotoxicity, blood cells, CF rats.*

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Effect of Oral Administration of Chloramphenicol on Hematological Profile of Male Charles Foster Rats

P. Shukla[α] & R. K. Singh[σ]

Abstract - For a given organism, relevant information about the internal environment can be easily accessed by its hematological profile. Chloramphenicol being a potent broad spectrum antibiotic is used readily in eyed drop formulations and is also in food industry. In the present study, varying doses (750, 1500 and 2250 mg/kg B.Wt) of Chloramphenicol (CAP) were administered orally as single daily dosage for 24 days to Male Charles Foster rats, to assess the hematological changes associated with oral exposure to the drug. The results showed a significant ($p<0.05$) dose dependent decrease in Red Blood Cells (RBC) count, Hemoglobin (Hgb), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin Concentration (MCHC) and increase in Hematocrit (Hct), White Blood Cells (WBC) and Platelets compared to the initial blood profile. The results recorded in this present study suggested that exposure to CAP results in Hematotoxicity. Hence, the potential of CAP to cause hematotoxicity is reported in the study.

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I. Introduction

Chloramphenicol (CAP) is a broad spectrum antibiotic, was first quarantined from bacterium *Streptomyces venezualae* in the year 1947. It was available by the trade name of Chloromycetin by Parke Davis & Co. It was prescribed in mass in 1948 in USA following an outburst of enteric fever. In 1949 it was cleared from Federal Food and Drug, since then it has been used and worked upon extensively being a potent inhibitor of protein synthesis (E. Cundliffe and K. McQuillen, 1967).

Some studies suggest the use of CAP in food. Although, most countries have banned CAP from animal food production, still traces of it have been detected in shrimp and other aquaculture products. According to regulations promulgated in 1980's and 1990's, use of CAP in food was banned and countries have established a zero tolerance policy. In Japan, zero tolerance thresholds for CAP is 50 ppb which in USA is 5 ppb. Meat and offal from treated animals contained CAP and its non – genotoxic metabolites (G. Milhaud, 1993).

Even being a potent antibiotic with a broad range of spectrum, the use of CAP is limited due to its association with aplastic anaemia (AA) (M. L. Rich, et al., 1950) and bone marrow suppression (C. E. Amberkar, et al., 2000). AA is a rare, dose independent, irreversible, idiosyncratic, manifestation of CAP which in most cases is seen years after the treatment (A. A. Younis, 1989 (a)) and is fatal (A. A. Turton, et al., 2002) risk of developing AA after CAP administration is 1:30000 to 1:5000015 (C. H. Li, et al., 2010). Only orally administered CAP leads to AA (R. Holt, 1967; R. A. Gleckman, 1975). This has made the CAP to be prescribed parenterally by many physicians. It is not known whether this lowers the incidence of AA or not but the risk is obviously lowered. Other than oral and parenterally absorbed CAP, it is also used as ophthalmic preparations where AA is also very rare (R. L. Rosenthal and A. Blackman, 1965; G. Carpenter, 1975; S. M. Abrams, et al., 1980)

Blood or hematological parameters are probably the more rapid and detectable variations under stress and are fuel in assessing different health conditions (V. Hymavathi and L. M. Rao, 2000). Hence, the significance of hematological parameters in clinical and experimental studies in life sciences cannot be overemphasized. Particularly, literature reports have proved that the alterations in the hematological parameters, from normal state/levels, may be used as valuable indicators of disease, or stress in different animal species (A. K. Solanke and V. Singh, 2000; B. K. Das and S. C. Mukherjee, 2003; L. H. Jee, et al., 2005; M. F. Rahman and M. K. Siddiqui, 2006; F. E. Uboh, et al., 2005).

Literature reports that hematological profile of different species of animals may be influenced adversely by phenylhydrazine (F. S. Sanni, et al., 2005; J. Berger 2005; S. K. Jain and D. Subrahmanyam, 1978), some antiretroviral drugs (A. A. A. Kayode, et al., 2011), Paclitaxel (J. A. Juaristi, et al., 2001), Carbamazepine (S. Thakur, et al., 2012), Doxorubicin (D. A. Eppstein, et al., 1989), Tetrachloroethylene (A. M. Emara et al., 2010), Phenacetin (C. B. Jensen and D. J. Jollow 1991) and Benzene (A. Beamonte et al., 2005; R. Synder and C. C. Hedli, 1996). Plants also have been shown to have ameliorative potential in reference to drug induced hematotoxicity (F. S. Sanni et al., 2005; E. E. Edet et al., 2011; E. V. Ikpeme et al., 2011; S. O. Kolawole et al., 2011, G. Prasad and G. L. Priyanka, 2011). Different

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extracts (methanolic, ethanolic, water, chloroform, hexane) of some plants namely, Hibiscus cannabinus (G. A. Agbor, et al., 2005), Brillantaisia nitens (P. A. Akah, et al., 2009(a), 2010(b)), Hibiscus sabdariffa (A. Ologundudu, et al., 2010), Zingiber officinale (A. M. M. Attia, et al., 2013), Ocimum basilicum (S. Saha. et al., 2012) and Ocimum gratissimum (A. W. Obianime, et al., 2011) have been reported to express a positive impact on the hematological profile of several animal species. Assessment of hematological parameters can therefore be useful in determining the extent of deleterious effects of foreign substances on the blood parameters of an animal. The present investigation was therefore aimed at assessing the effect of Chloramphenicol on the hematological profile in Charles Foster male rats.

II. Materials and Methods

a) Administration of Material

The chloramphenicol Capsules IP manufactured by Piramal Health Care Limited (Batch No-9BE012) were used for the study. Freshly prepared chloramphenicol suspension was administered orally by cannula for 24 days.

b) Animals

Albino rats of *Charles Foster* strain were used in the study. IAEC approval number was taken from the Institutional Animal House Facility which is affiliated to and works under the guidelines of CPCSEA (No. 36/11/Toxicol/IAEC). Rats weighed between 120- 150 grams and were housed in polypropylene, autoclavable cages (dimensions: 43x27x15 cm) with steel wire-mesh lid having provisions for attaching water bottle and for keeping food pellets. Animals had continuous access to food and water during the entire period of experimentation. They were examined routinely for their body weights and hematological parameters.

c) Experimental Design

20 rats showing evidences of good health were selected on the basis of findings of their initial health check-up and body weight recordings. They were randomly assigned to four treatment groups, each group consisting of five male animals and one group comprising of an equal number of animals served as control.

Group I: Control (Distilled water)
Group II: Low Dose (750 mg/ kg B.wt CAP)
Group III: Mid Dose (1500 mg/ kg B.wt CAP)
Group IV: High Dose (2250 mg/ kg B.wt CAP)

d) Hematological Investigations

Blood collected from the caudal vein of experimental animals was assessed for all hematological parameters RBC (Red Blood Cell), Hgb (Hemoglobin), MCV (Mean Corpuscular Volume), MCHC (Mean Corpuscular Hemoglobin Concentration), Hematocrit (Hct), White Blood Cells (WBC) and Platelets. Blood analysis was performed at regular time intervals using fully automatic hematology analyzer MS-9. (Make/Model of Analyzer: MS-9 (Mellet Schloesing). Standard chemicals and reagents supplied by company were used.

e) Statistical Analysis

All data was analyzed by applying One way ANOVA with the *p value* limits of 0.05. Software used for the purpose was PRISM.

III. Results

The result of this study, on the effect of oral dosing of CAP on the hematological parameters in rats is presented in Table 1 and 2. The results showed that the hemoglobin (Hgb), Red Blood Cells (RBC) count, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin Concentration (MCHC) obtained for rats administered with CAP orally were significantly ($p<0.05$) lower in a dose-dependent pattern, compared to the control (Tables 1 and 2). On the contrary, the total White Blood Cells (WBC), platelets and Hematocrit (Hct) levels obtained for rats administered with CAP orally following the same pattern, were significantly ($p<0.05$) higher, compared to the control.

Table 1 : Initial Hematological Profile of CF rats

Gp	Treatment	Hgb	RBC	Hct	MCV	MCHC	WBC	Platelets
Gp. I	Control, D.W.	11.88±0.51	7.09±0.54	44.44±2.68	62.80±2.29	26.70±0.67	7.02±1.15	530.00±112.84
Gp. II	750 mg/g b.wt	12.30±0.51	6.97±0.69	46.22±5.57	66.28±3.87	26.78±2.64	9.93±2.05	331.00±145.74
Gp. III	1500 mg/kg b.wt	12.92±0.26	7.81±0.75	52.18±3.44	66.96±2.88	24.74±1.13	10.70±2.79	339.00±162.06
Gp. IV	2250 mg/kg b.wt	12.52±0.63	7.65±0.68	48.82±3.99	63.88±1.65	23.98±5.35	10.40±3.60	391.00±52.72

Data are presented as Mean±S.D., n=5, $p< 0.05$ compared to control.

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Table 2 : Hematological Profile of CF rats after oral administration of Chloramphenicol for 24 days

Gp	Treatment	Hgb	RBC	Hct	MCV	MCHC	WBC	Platelets
Gp. I	Control, D.W.	10.42±0.30	6.96±0.38	50.48±2.53	56.42±2.27	24.62±1.39	17.94±3.62	560.20±126.80
Gp. II	750 mg/kg b.wt	11.62±0.57	5.67±0.57	55.82±5.14	58.48±1.73	24.98±0.92	16.92±3.81	339.40±28.38
Gp. III	1500 mg/kg b.wt	10.12±1.29	7.20±0.75	55.28±5.14	60.12±2.37	22.96±1.63	17.58±5.27	419.40±127.18
Gp. IV	2250 mg/kg b.wt	11.26±0.40	6.24±0.75	51.98±3.73	56.32±2.24	23.64±1.11	17.12±3.34	397.40±9.63

Data are presented as Mean±S.D., n=5, p< 0.05 compared to control.

IV. Discussion

Hematological profiles are known to provide important information about the internal environment of a given organism. The results of this present investigation showed that oral exposure to CAP caused a significant decrease in Hgb, RBC, MCV and MCHC, whereas increase in Hct, WBC and Platelets. Similar effects on hematological parameters have been reported for such other drugs as Chlorpyrifos (Y. Savithri et al., 2010), Thiodan 35 E.0 (A. K. Solanke and V. H. Singh 2000), Chloropharm (T. Fujitani et al., 2001), Endosulfan (N. Choudhary and S. C. Joshi, 2002) and Lindane (M. D. A. Baig, 2007) and Deltamethrin (S. H. Kowalczyk-Bronisz, et al., 1990). The hematotoxic condition may results from different mechanisms, including decrease in the rate of blood cells synthesis and/or increase in the rate of blood cells destruction. The observed decrease in RBC count, Hgb, MCH and MCHC may therefore, may assumed to be associated with retarded hemopoeisis, destruction and shrinkage of RBC.

Increase in total white blood cells and platelets, as well as increase in Hct, is also reported in this study. The increase in total white blood cells and lymphocyte observed in this work may be suggested to be due to stimulated lymphopoiesis and/or enhanced release of lymphocytes from lymph myeloid tissue (B. K. Das and S. C. Mukherjee, 2003). This lymphocyte response might be a direct stimulatory effect of toxic substances on lymphoid tissues. Alternatively, this response may be assumed to be associated with the drug induced tissue damage and disturbance of the non-specific immune system leading to increased production of leukocytes.

Researchers have reported that CAP induce and enhances some defects which results in damage to undifferentiated marrow stem cells (E. P. Cronkite, 1964). Other researchers suggested that certain enteric bacteria can produce a specific enzyme that degrades CAP to a toxic product (R. Holt, 1967). This was suggested by further studies, which suggests that the metabolites of CAP generated by intestinal bacteria undergo further metabolic transformations in system with *in situ* production of toxic intermediate (A. A. Yunis, 1989 (a)). In a study (A. A. Yunis, 1973 (b)) it was actually revealed that the p-nitrosulfathiazole group is responsible for CAP induced hematotoxicity by inhibiting DNA synthesis in marrow stem cells. This theory was based on the observation that thiamphenicol which is a CAP derivative, does not have a p-nitrosulfathiazole group and does not cause hematotoxicity and thus, extensively used in Europe. This theory was further supported by studies indicating CAP reduced to p-nitrosulfathiazole which is a short lived reduction intermediate and leads to helix destabilization and strand breakage (M. Irena, et al., 1983) except than being unstable these intermediates are highly toxic (P. Eyer, et al., 1984). At a concentration of 2000-4000 μg/ml CAP depressed phagocytosis and burst activity of neutrophils (M. J. Paape, et al., 1990). Other studies suggests that CAP directly induce apoptosis in hematopoietic stem cells, directly leading to hematotoxicity (C. I. Kong, et al., 2000).

V. Conclusion

In conclusion, significant adverse changes in hematological parameters are reported to be associated with exposure to CAP, in this present study. This therefore suggest that exposure to CAP may be considered to be among the risk factors for the development of anaemic condition. Hence, exposure to this drug should be minimized.

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Evaluation of the Anti-Inflammatory Effects of *Blumea Aurita*

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Abstract - *Background :* There are repeated evidences suggesting potential therapeutic effects of *Blumea aurita*; however, the literature lacks scientific proofs for these benefits.

Aims : 1) to determine phytochemical constituents of *Blumea aurita*, 2) to evaluate anti-inflammatory, anti-pyretic and analgesic effects of *Blumea aurita* 3) to assess the membrane stabilizing activity of *Blumea aurita* as a possible mechanism for its therapeutic effects.

Material and Methods : Phytochemical constituents were determined according to the standard methods. A series of experiments were conducted in animal models using Wister albino rats to evaluate the possible effects of *Blumea aurita*. Edema-inhibition percent (EI %) and granuloma tissue-formation inhibition (GTI %) were used to evaluate anti-inflammatory effects, the hot plate method to assess analgesic effects and inhibition percent of heat-induced and hypotonic solution-induced RBCs haemolysis to determine membrane stabilizing activity.

Results : The phytochemical screening of *Blumea aurita* revealed presence of triterpenes, flavonoids, saponin, cumarins, tannins and traces of alkaloids. The herb is devoted from unsaturated sterols and anthraquinon. Experimental evaluation of the anti-inflammatory effects of *Blumea aurita* revealed highest EI % after 4 hours of oral administration of *Blumea aurita* extract at a dose of 400 mg/kg (EI% = 53%), and 6 hours at 800mg/kg (EI% = 67%).

Conclusion : The current results strongly suggest anti-inflammatory, anti-pyretic, analgesic and membrane stabilizing effects of *Blumea aurita*. The relevance of the potential therapeutic effects of *Blumea aurita* to its phytoconstituents was discussed.

Keywords : *analgesic, anti-inflammatory, antipyretic, blumea aurita, membrane stabilizing activity.*

GJMR-B Classification : *NLMC Code: WB 330*

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Conclusion : The current results strongly suggest anti-inflammatory, anti-pyretic, analgesic and membrane stabilizing effects of *Blumea aurita*. The relevance of the potential therapeutic effects of *Blumea aurita* to its phytoconstituents was discussed.

Keywords : analgesic, anti-inflammatory, antipyretic, blumea aurita, membrane stabilizing activity.

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I. Introduction

Blumea aurita (Synonyms: *Laggera aurita*; local name: Raihan Aljroof) belongs to the family Asteraceae which is one of the longest families of flowering plants. The family is of worldwide distribution and particularly well represented in semi-arid regions of the tropics and subtropics [1]. It is pubescent pale herbs up to 1m high, strongly scented herb [2]; strongly unpleasant aromatic [3] or aromatic herb [4], erect or decumbent annual herbs. Leaves alternate sessile, oblong-obovate, auriculate and interruptedly decurrent, margin dentate. It is inflorescences compound monochasial heads, 5-6, 7-8 mm; head heterogamous, outer florets filiform, inner one tubular. Its Habitat is water catchments areas. It is found in Central and Southern Sudan [4], mainly in Rahad, Nile Bank and Khartoum.

There are no previous phytochemical reports on *Blumea aurita*; however, flavones, flavonoids, essential oils and organic acids were reported from various *Blumea spp*. [5]. The boiled water extract of the leaves is used for jaundice [6]. The antibacterial activity of seven essential oils of *Laggera aurita* has been studied [4, 5, 7].

Blumea aurita is used in traditional medicinal practice by Sudanese healers to treat; pain; and rheumatism. There were no previous studies in the possible anti-inflammatory, antipyretic or analgesic effects of this plant.

There were repeated evidences that support potential therapeutic effects of *Blumea aurita*. In eastern Sudan, *Blumea aurita* was used by traditional Sudanese herbalists for the treatment of connective tissue inflammatory conditions, pain, fever and jaundice. However, the present literature lack any scientific proofs for these therapeutic benefits. The aims of this study were to screen for the possible phytoconstituents of *Blumea aurita* and to evaluate its anti-inflammatory, anti-pyretic and analgesic effects. In addition, the membrane stabilizing activity of *Blumea aurita* as a possible mechanism for its therapeutic benefits was also evaluated.

II. Experimental

a) Collection and extraction of plant materials

The whole plant was collected from Kasala in Eastern Sudan; after it had been authentificated by

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taxonomists of Medicinal and Aromatic Plants Research Institute (MAPRI) - Sudan. A sample was deposited at the herbarium in the institute. The plant material was then allowed to dry at room temperature for three days. Then the plant material was coarsely powdered.

The dried coarsely powdered plant material was extracted using the soxhlet apparatus. The extraction was first run by petroleum ether to extract the fats and fatty constituent; then by chloroform to separate the non polar compounds; and finally by 70% ethanol to separate the polar compounds. The ethanolic extract was evaporated to dryness under reduced pressure, and kept into a refrigerator to be used for the different tests.

b) Animals

Adult male and female Wister albino rats weighing 90-200 g (a total of 230 rats), were purchased, at the time of each experiment, from the animal center of MAPRI, National Center for Research, Khartoum. All animals had free access to food and water and were kept at room temperature 25±1 ^{o}C, on a 12/12 light/dark cycle. Before each study, animals were submitted to fasting for at least 12 hours.

c) Phytochemical screening

i. *Test for unsaturated sterols and triterpenes*

One ml chloroform was added to the ethanolic extract, and then 0.5 ml of acetic acid anhydride was added followed by 2 drops of concentrated sulphuric acid. The gradual appearance of green, blue, pink to purple color was taken as an evidence of the presence of sterols (green to blue) and triterpenes (pink to purple) in the sample.

ii. *Test for alkaloids*

Five ml of 2N hydrochloric acid were added to 0.5 gm of the extract and stirred while heating in a water bath for 10 minutes. The mixture was cooled, filtered and divided into two test tubes. Few drops of Mayer's reagent were added to one test tube. Few drops of Velser's reagent were added to the other tube. A slight turbidity or heavy precipitate in either tube was taken as presumptive evidence for the presence of alkaloids

iii. *Test for flavonoids*

Half gram of the ethanolic extract of the plant was dissolved in 1 ml ethanol and then 1 ml of 1% KOH was added. Dark yellow color indicates the presence of flavonoids. For conformation, 1 ml of aluminum chloride was added to the extract. Appearance of yellow color confirms presence of flavonoids.

iv. *Test for saponin*

One ml of distilled water was added to the extract in a test tube and was shacked. Formation of foam is considered positive for the presence of saponin.

v. *Test for cumarins*

Half gram of the extract was added to 20 ml of distilled water and boiled. A filter paper was attached to the test tube to be saturated with the vapor then a spot of 0.5 N KOH was put on it. The filter paper was inspected under ultraviolet light. Adsorption of ultraviolet light confirms presence of cumarins.

vi. *Test for anthraquinon*

Half gram of the extract was boiled in 10 ml of 0.5 N KOH containing 1 ml of 3% hydrogen peroxide solution. The mixture was shaken with 5 ml benzene, and allowed to separate into two layers, and then 3 ml of 10% ammonium hydroxide solution were added. The presence of anthraquinones was indicated if the alkaline layer was changed to pink or red color.

vii. *Test for tannins*

Ten ml of hot normal saline were added to 1 gm of the extract and allowed to cool, and then gelatin salt reagent was added to 5ml of the mixture. Immediate precipitation was considered positive for the presence of tannins. In addition, ferric chloride test reagent was added to the other 5 ml of the mixture, Blue, black or green colors were considered positive for the presence of tannins.

d) Evaluation of anti-inflammatory activity

i. *Rat-paw edema model*

The anti-inflammatory activity of ethanolic extract was studied using a modification of rat paw formalin edema method as described by Domenjoz *et. al* [8] and Ramadan *et. al* [9]. The anti-inflammatory effect was determined after measuring the paw's thickness before the formalin injection, and then 1, 2,3,4,6, and 24h post-treatment [9]. The inflammatory response to formalin was evaluated by:

1. Mean paw thickness (MPT) in mm: the mean of the increase in paw thickness after inducing inflammation by formalin.
2. Edema inhibition percentage (EI %) [10]: EI is calculated based on edema formation percentage as follows:

$$\text{Edema formation percentage (EF\%)} = \frac{\text{Tt_To}}{\text{To}} \times 100$$

$$\text{Edema inhibition percentage (EI\%)} = \frac{\text{EFc_EFt}}{\text{EFt}} \times 100$$

Where:

- To = the paw thickness before formalin injection (mm)
- Tt = the paw thickness after t hours of formalin injection (mm)
- EFc = edema formation rate of the control group
- EFt = edema formation rate of the treated group at t hours time

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The observations were statistically analyzed using analysis of variance followed by multiple comparisons [11, 12] via SPSS program

ii. *Cotton pellet granuloma-formation inhibition method*

The method described by Goldstain et al [13] was employed. Cotton pellet weighing 500mg were sterilized in an autoclave. The cotton pellet was implanted subcutaneously in the groin region of each rat under light ether anaesthesia. The cavity was stitched to avoid the drop out of the pellet and exudates. The groups were then orally dosed with aqueous suspension of the ethanolic extracts of Blumea aurita, indomethacin and normal saline once a day as follows:

- Group 1 (N = 5 rats): Blumea aurita 800mg/kg
- Group 2 (N = 5 rats): Blumea aurita 400mg/kg,
- Group 3 (N = 5 rats): Indomethacin 5mg/kg.
- Group 4 (N = 5 rats): normal saline 1ml/kg (control group)

The treatment continues for 5 consecutive days. On day 6 the rats were scarified under light ether anesthesia, the pellets were separately removed and the extraneous materials were removed. The pellets were allowed to dry in an oven at 60 °C overnight. The cotton pellets were weighed individually and the increase in weights were calculated, and considered as the granuloma tissue deposits. Values of granuloma tissue weight were expressed as means ± standard error of the mean (S.E.M).

The mean increase in cotton-pellet weight of the control group was considered as 100% and the rest groups were compared to it as follows:

$$\text{Granuloma tissue formation inhibition percentage(GTI\%)} = \frac{C0_C1}{C0} \times 100$$

Where;

- C0 = the mean of the differences of the control group
- Ct = the mean of the differences of the treated group

Statistical analysis was determined using ANOVA followed by Dunnett's test for multiple comparisons and was employed via SPSS program.

e) Analgesic Activity

The hot plate method as described by Jacob and Bosvski [14] was adopted. The groups were then orally dosed with aqueous suspension of the ethanolic extracts of Blumea aurita, indomethacin and normal saline once as follows:

- Group 1 (N = 5 rats): Blumea aurita 800mg/kg
- Group 2 (N = 5 rats): Blumea aurita 400mg/kg,
- Group 3 (N = 5 rats): Asprin 100mg/kg.
- Group 4 (N = 5 rats): normal saline 1ml/kg (control group)

The rats were dropped on a hot plate maintained at 55 ± 0.50C. The response time was defined as the interval from the instant the animal reached the hot plate until the moment the animal licked its feet or jumped out. The response time was recorded at 10 minutes before treatment, 5 minutes before treatment, 60, 90, and 150 minutes after treatment (using the Hot plate model 39, Wagtech International Ltd - England). Statistical analysis was determined using ANOVA followed by Dunnett's test for multiple comparisons.

f) Antipyretic activity

Hyperpyrexia was induced in rats by subcutaneous administration of 20 ml/kg of 20% aqueous suspension of Brewer's yeast [15]. The rat groups were then orally dosed with aqueous suspension of the ethanolic extracts of Blumea aurita, indomethacin and normal saline once as follows:

- Group 1 (N = 5 rats): Blumea aurita 800mg/kg
- Group 2 (N = 5 rats): Blumea aurita 400mg/kg,
- Group 3 (N = 5 rats): Asprin 100mg/kg.
- Group 4 (N = 5 rats): normal saline 1ml/kg (control group)

Temperatures were then recorded 5 min before and 1, 2 and 4 hours after treatment using Themalert model No.TH5 (Physitemp -U.S.A). Statistical analysis was determined using ANOVA followed by Dunnett's test for multiple comparisons and was employed via SPSS program.

g) Assessment of membrane stabilizing ability

The membrane stabilizing activity of *Blumea aurita* was evaluted according to Shinde *et al.* [16] and Abe *et al.* [17]. Erythrocytes were separated from untreated control rats and suspended in 10mM Na_3PO_4 as 40%. Membrane stabilizing ability was determined as follows:

i. *Heat-induced haemolysis*

5 ml of the isotonic solution (10mM sodium phosphate buffer) containing 50, 100, and 200μg/ml of ethanolic extract of *Blumea aurita* were put into two duplicate sets of centrifuge tubes. 5 ml of the isotonic buffer serve as a control. Erythrocyte suspension (30μl) was added to each tube and mixed gently. One pair of the tubes was incubated at 54 °C for 20 min in a water bath. The other was maintained at 0-5 °C in an ice bath. The reaction mixtures were centrifuged and optic

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densities of the supernatant were measured at 540nm using UV-160A spectrophotometer. Optic density of each solution was used as an indicator for the degree of hemolysis and hence cell membrane stability. Acetyl salicylic acid (aspirin) 200μg/ml was used as a reference standard.

ii. *Hypotonic solution-induced haemolysis*

Same as described above but using hypotonic solution (154mM NaCl), erythrocyte suspension (30μl) was mixed with 5 ml of the hypotonic solution containing *Blumea aurita* ethanolic extracts at concentrations of 50, 100, and 200 μg/ml. The control sample was mixed with drug free solution. The mixtures were left for 10 minutes at room temperature and centrifuged for 3 min at 1300g. Optic density of each solution was measured and used as an indicator for the degree of cell membrane stability. Acetyl salicylic acid (aspirin) 200μg/ml was used as a reference standard.

In experiment, the percentage inhibition or acceleration of haemolysis were calculated according to the equation:

$$\% \text{ Acceleration or inhibition of haemolysis} = \left(1 - \frac{OD2 - OD1}{OD3 - OD1}\right) 100$$

Where:

- OD_1=test sample unheated or in isotonic solution;
- OD_2= test sample heated or in hypotonic solution;
- OD_3=control sample heated or in hypotonic solution.

Statistical analysis was determined using ANOVA followed by Dunnett's test for multiple comparisons.

III. Results

The findings of the phytochemical screening of the of *Blumea aurita* revealed presence of triterpenes, flavonoids, saponin, cumarins, tannins and traces of alkaloids. In contrast, *Blumea aurita* is devoted from unsaturated sterols and anthraquinon (table-1). Table-2 shows the effects of ethanolic extracts of *Blumea aurita* and indomethacin on rat MPT and EI% at the studied time intervals. The highest EI% for both indomethacin and *Blumea aurita* at a dose of 400mg/kg were reported after 4 hours of oral administration of the aqueous suspension. *Blumea aurita* at a dose of 800mg/kg showed a peak EI% after 6 hours (tabl-2). The effects of ethanolic extract of *Blumea aurita* was dose-dependent reduction in MPT and EI%. As shown in table-3, granuloma tissue-formation inhibition percentage of *Blumea aurita* at a dose of 800mglkg (63.79%), and *Blumea aurita* at 400mg/kg (56.72%) were significantly more compared to indomethacin (32.25%). The peak rats' response to analgesia was recorded after 60 minute of oral administration of *Blumea aurita* in a dose-dependent manner (table-4). *Blumea aurita,* at a dose of of 800 mg/kg, significantly reduced body temperature of hyperthermic rats compared to acetylsalicylic acid; however, there was no significant difference between acetylsalicylic acid and *Blumea aurita* at a dose of 400 mg/kg (table-5). *Blumea aurita* ethanolic extracts at a concentration of 50μ/ml, 100μ/ml, 200μ/ml, showed significant inhibition of heat-induced and hypotonic solution-induced red cell hemolysis compared to acetylsalicylic acid at 200μ/ml concentration, (table-6, $P < 0.05$ using Dunnett test).

Table 1 : Phytoconstituents of the ethanolic extracts of *Blumea aurita*

Blumea aurita	Ingredients
Negative	Unsaturated sterols
Positive	Triterpenes
Traces	Alkaloids
Positive	Flavonoids
Positive	Saponin
Positive	Cumarins
Negative	Anthraquinon
Positive	Tannins

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Table 2 : Effects of ethanolic extracts of B. aurita and indomethacin on rat paws' thickness and edema inhibition percentage at studied time intervals

Extract/drug		Time interval						Mean
		1 hour	2 hours	3 hours	4 hours	6 hours	24 hours	
B. aurita	EI%	41.6	59.5	47.2	52.8	99.86*	95.6	67
(800 mg/kg)	MPT(mm)	7.41±.31	6.51±.21	6.51±.37	5.29±.22	5.88±.28	5.36±.14	6.03±.79
B.aurita (400mg/kg)	EI%	48.92	51.8	24.83	87.31*	46.21	68.87	53.15
	MPT(mm)	7.16±.39	6.84±.33	7.30±.15	5.83±.31	7.05±.12	5.71±.35	6.43±.85
Indomethacin	EI%	24.2	32.2	50.9	97*	83.4	71.4	64
(5mg/kg)	MPT(mm)	8.29±.64	7.59±.39	6.67±.52	5.63±.33	5.91±.25	6.05±.17	6.52±1.06
Normal saline	EI%	9.03±.71	8.45±.39	7.71±136	8.24±.41	7.69±.32	7.21±.20	7.68±1.15

* The highest edema-inhibition percentage.

Table 3 : Granuloma tissue formation inhibition percentage for *B. aurita* ethanolic extracts and indomethacin

Extract/drug	Granuloma weight (mg) Mean±SEM	Percent inhibition
B. aurita (800 mg/kg)	42.67±.71	63.79%
B.aurita (400mg/kg)	51±2.27	56.72%
Indomethacin (5mg/kg)	79.83±4.46	32.25%
Normal saline	117.83±.60	

Table 4 : The analgesic effect of B. aurita ethanolic extracts and acetylsalicylic acid

Extract/drug	Mean response time /time interval					Mean response time /time interval
	10 minutes before treatment	10 minutes before treatment	10 minutes before treatment	10 minutes before treatment	10 minutes before treatment	
B. aurita (800 mg/kg)	6.89	7.51	22.09	18.87	11.84	13.43±.1.15
B. aurita (400 mg/kg)	7.48	8.26	18.58	14.94	9.45	11.76±9.89
Acetylsalicylic acid (100 mg/kg)	7.91	10.91	13.42	11.68	9.24	10.63±0.57
Normal saline	6.75	7.87	16.88	14.19	10.19	5.49±0.20

Table 5 : Antipyretic activity, mean rectal temperature at intervals for rats treated with B. aurita ethanolic extracts and acetylsalicylic acid

Extract/drug	Body temperature/interval (°C)				mean±SEM (°C)
	Before treatment	1hour after treatment	2h0urs after treatment	4hours after treatment	
B. aurita (800 mg/kg)	39.06±0.46	36.28±0.07	36.24±0.16	36.37±0.14	36.83±0.14
B. aurita (400 mg/kg)	39.36±0.42	36.36±0.11	36.38±0.1	36.29±0.11	37.08±0.16
Acetylsalicylic acid (100 mg/kg)	39.44±0.3	36.58±0.27	36.36±0.06	36.39±0.11	37.32±0.17
Normal saline	38.7±0.81	38.24±0.34	38.9±0.44	37.46±20.29	38.46±0.14

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Table 6 : Membrane stabilizing ability percentage inhibition of RBCs haemolysis produced by *B. aurita* ethanolic extracts and acetylsalicylic acid

Extract/Drug	Concentrations	Heat-induced haemolysis % inhibition Mean%±SEM	Hypotonic solution-induced haemolysis % inhibition Mean%±SEM
B.aurita	50 µg/l	27.73±.19*	67.91±.82*
	100 µg/l	48.74±.80*	79.61±.84*
	200 µg/l	65.60±99*	91.86±1.88*
Aspirin	200 µg/l	25.19.28	76.41±.61

IV. Discussion

The findings of the current study give scientific confirmation for the anti-inflammatory, anti-pyretic and analgesic effects of *Blumea aurita*. These effects are probably attributed to the unique phytoconstituents of *Blumea aurita* which deserve further investigations. Interestingly, the effects of *Blumea aurita* exceed the classical non-steroidal anti-inflammatory drugs (NSAID) used in clinical practice, namely indomethacin and acetylsalicylic acid. *Blumea aurita* was used by traditional Sudanese herbalists for the treatment of many inflammatory conditions, including rheumatoid arthritis, and for pain relief. However, the plant did not receive any scientific attention, and the results of the current study represent the first report on the possible therapeutic effects of *Blumea aurita*.

The phytochemical screening of *B.aurita* revealed presence of triterpenes, Alkaloids, Flavonoids, Saponins, Cumarins and Tannins; however, the plant is devoid of unsaturated sterols and Anthraquinon. The existence of flavonoids in the *Blumea aurita*, may account for the observed anti-inflammatory activity [18, 19]. Fan *et al* [20] attributed the anti-inflammatory activity of *Terminalia catappa* to triterpenic acids, and since *Blumea aurita* contains triterpens this finding may be applied to it. In addition, the current results showed significant granuloma tissue formation inhibition, indicating that the *Blumea aurita* has the ability to interfere with one or more responses of the inflammatory processes especially those concerned with the inflammatory cells migration and proliferation. The reduction in granuloma tissue weight could be due to better maturation of collagen which invariably leads to shrinkage of granulation tissue [22].

The analgesic activity of *Blumea aurita* may in part be attributed to the saponine, triterpenes, sterols, flavonoids and glycosides [9]. . In the folklore medicine of different cultures, the plants rich in triterpenes are commonly used for the treatment of inflammation [23]. Although it is not possible to pin point the exact phytoconstituent(s) responsible for the anti-inflammatory, anti-pyretic and analgesic activities, these effects appear to be due to the flavonoids or glycosides as well. Actually, these later two phytoconstituents were present in *Caralluma tuberculata* when studied by Ahmed *et al* and can elucidate the anti-inflammatory and analgesic effects of this herb [23]. Alternatively, Ramadan *et al* [9] studied the anti-inflammatory, analgesic of *Adansonia digitata* and reported that the anti-inflammatory effect may be due to the presence of sterols, saponins and triterpenes in their aqueous extract, same as *Blumea aurita*.

On the other hand, according to the current data *Blumea aurita* possess antipyretic activity more than acetylsalicylic acid at a dose rate of 100 mg/kg. The *Blumea aurita* is also rich in saponins which explain its antipyretic activity as proved by Mohsin *et al* [15] when studying therapeutic effects of *Tamarix nilotica*.

The plant significantly reduced erythrocytes heat-induced and hypotonic solution-induced haemolysis compared to acetylsalicylic acid at a concentration of 200µm/L. According to Abe *et al* [17], saponins are claimed to have a membrane stabilizing action. The possible explanation for the membrane stabilizing activity could be an increase in the surface area/volume ratio of the cells which could be brought about by an expansion of membrane or shrinkage of the cell by interacting with certain cytoskeletal proteins [17, 24]. Theoretical speaking, the membrane stabilizing activity of *Blumea aurita* interferes with the release of the mediators of inflammation, fever and pain producing substances and therefore explain the therapeutic effects of *Blumea aurita* [24].

In conclusion, the current data prove beyond doubt the potential therapeutic effects of *Blumea aurita* in treating acute inflammation as indicated by edema inhibition, chronic inflammation as indicated by inhibition of granuloma tissue formation, pain and hyperpyrexia. In addition, current results augment what was acknowledged by traditional Sudanese herbalists that *Blumea aurita* is an effective treatment of many inflammatory conditions, including rheumatoid arthritis. Detailed phytochemical and toxicological investigations are desirable to determine the active ingredients responsible to the therapeutic effects of *Blumea aurita* and the potential side effects.

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Pre-Emptive Intravenous Paracetamol and Lornoxicam in Third Molar Surgery

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Abstract - *Backgrounds:* The objective of the present study was to compare the postoperative analgesic effects of pre-emptive intravenous (IV) paracetamol, lornoxicam and placebo following third molar surgery.

Materials and Methods: This was a prospective, double-blind, randomized, placebo-controlled study where 50 patients had both of their identical impacted mandibular third molars impacted. Before the removal of the impacted third molar tooth on one side either of the two drug regimens (1g paracetamol or 8 mg lornoxicam) administered preemptively and 15 days later second surgical approach was performed but this time for comparison the other drug regimen (which was not chosen initially) was carried out as the preemptive agent; and all of the operations were performed by the same surgeon. Diclofenac sodium up to 75 mg daily was provided as rescue medication. The postoperative rescue analgesic consumption was recorded and pain scores were evaluated with a Verbal Rating Scale (VRS) at 15,30 min and 1,2, 4, 6, 12, 24 h postoperatively.

Results: There was a significant difference in mean second hour VRS scores between paracetamol and lornoxicam group in favor of the lornoxicam ($p<0.05$). But, conversely, there was no statistically significant difference in the need of use and the consumption of rescue analgesic medication between two drug groups.

Conclusion: Pre-emptive IV paracetamol and lornoxicam effectively decreased the pain scores as compared to placebo in third molar surgery.

Keywords : *third molar; pre-emptive analgesia; lornoxicam; paracetamol.*

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Pre-Emptive Intravenous Paracetamol and Lornoxicam in Third Molar Surgery

Esra Cagiran [α], Can Eyigor [σ], Bahar Sezer [ρ] & Meltem Uyar [ω]

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I. Introduction

Third molar surgery is frequently performed by maxillo-facial and dental surgeons. In the postoperative period mild to moderate pain is the most common complaint observed [1] Postoperative pain induces long-term changes in both central and peripheral nervous systems.[2] Induction of cyclooxygenase and consequent prostaglandin release results in localized long term hyperalgesia, due to sensitization of peripheral nociceptors.[3] Preemptive analgesia, first defined by Woolf in 1983, was shown to decrease the duration and intensity of postoperative pain.[4] It has been shown that analgesic agents applied before the injury remarkably decrease postoperative pain in comparison to the analgesics given afterwards, related to the desensitization of central neural system.[5]

Non-steroid anti-inflammatory drugs (NSAIDs) used before the operation avert the progression of pain by inhibiting early inflammatory mediator synthesis and desensitization of the nervous system. Lornoxicam is a NSAID which decreases prostaglandin synthesis by inhibiting cyclooxygenase. It has analgesic, antipyretic and anti-inflammatory effects. The short plasma half-life of lornoxicam (approximately 4 hours) may provide advantages over other NSAIDs, which were convicted previously for having a higher incidence of adverse effects because of their long plasma half-lives.[6]

Hein and colleagues[7] showed that use of prophylactic lornoxicam markedly abates the pain in and after the minor surgical approaches. Pektas et al.[8] found that 16 mg preemptive oral use of lornoxicam, seems to be effective in postoperative management of pain after third molar surgery.

On the other hand, as an antipyretic non-opioid analgesic, paracetamol is drastic in mild to moderate pain.[9] Even though the exact mechanism of action is still unknown being speculated that its primary effect is carried out by the inhibition of early prostaglandin synthesis in central nervous system. According to the evidence-based medical literature, paracetamol is one of the most important analgesic agent in pain management for patients having jaw surgery.[10] Hovewer, it is out of its particular value when NSAIDs are contraindicated, perhaps by a known hypersensitivity or a history of gastrointestinal ulceration or bleeding.[11]

The onset of analgesic action is an significant factor, in terms of the clinical efficacy for a drug especially in the management of postoperative pain. Patients having surgery crave for an effective and fast-acting pain relief. The oral application is not effective and sometimes not possible if rapid analgesia is needed, which is often frequent after such a surgery. Therefore, intravenous (IV) administration is the route of choice.[12] with recent introduction of IV forms of lornoxicam and paracetamol, effective consequences have been obtained in postoperative pain management. Accordingly, our study aimed to compare the effects of preemptively used IV forms of lornoxicam and paracetamol, on postoperative pain in patients (cases-da kullanılabilir) undergoing bilateral lower third molar surgery.

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II. Material and Methods

The study were designed as a randomized, placebo-controlled and prospective process and performed in Department of Oral and Maxillofacial Surgery of the Faculty of Dentistry of Ege University following the approval of the Ethics Committee of Ege University Faculty of Medicine. Written informed consent was obtained from 50 ASA physical status I outpatients (aged 18–35 years), undergoing the surgical removal of bilateral impacted third molars.

The sequence of drug administration was determined randomly by computer.

As the basic selection criteria, patients having bilaterally impacted lower third molars with the same anticipated degree of extraction difficulty were included; and the cases whom voluntarily signed up their written informed consents were enrolled to this study.

Impacted third molars were confirmed with panoramic radiograms, and according to their radiologic examination cases seems to be in Class II Position-B under Pell-Gregory classification[13] (Table1) were included.

Exclusion criteria included known allergy or sensitivity to any NSAID and local anesthetics.

History of asthma or chronic obstructive pulmonary disease, blood dyscrasia or coagulation disorders, cardiac insufficiency or gastrointestinal disease, renal and hepatic insufficiency, and pregnancy. Patients were not allowed to receive any analgesic within 24 hours prior to operation.

Those were also excluded from the study; who developed alveolitis, postoperative infection, numbness and trismus in 15 days between two extractions in order not to effect the evaluation of postoperative pain.

a) Study Design

As the initial surgical approach, one of the bilateral impacted lower third molar teeth was removed with using either of two drugs being assessed preemptively and then with an interval of 15 days the tooth on the contrlateral side was removed at the second appointment with the preemptive administration of alternative analgesic agent (split-mouth design). Each patient received a single IV pre-emptive dose of either 1000 mg of paracetamol or 8 mg oflornoxicam, 15 minutes prior to surgery. Although the surgeon and study staff remained blinded to the treatment group by pre-packaging of the drugs had been studied, the patients had full knowledge of the analgesic agent which had been used, as they were prescribed the medications before operation. On the other hand, patients in control group were exposed to operation for one of lower third molar each.

All drugs dissolved in 100 ml of 0.9% NaCl and then administered via IV infusion in 15 minutes. After the drug infusion, all operations were performed by the same surgeon in a standardized manner under local anesthesia (inferior alveolar, lingual and buccal nerve blocks maintained by 2 ml of articaine hydrochloride 40 mg/ml with epinephrine HCl; 0.006 mg/ml for each case). The surgical procedure was standardized and involved creation of triangular mucoperiosteal flap followed by bone removal using a drill cooled with water. After extraction, the wound was rinsed with a sterile saline solution and achieving local haemostasis, the wound was sutured.

Diclofenac sodium up to 75 mg (oral dose of 25 mg 3 times daily) was supplied as rescue medication for patients who did not achieve adequate analgesia (VRS $\geq$2) with preemptive administration. In addition the use of rescue analgesic was not permitted within 2 hours following the operation.

All patients were discharged at 1 h after the surgery and asked to complete a questionnaire. The questionnaire had comprised VRS and a survey concerning the effects of postoperative pain on patients' physical and social activities, including the consumption of solid food, speech, sleeping, maintenance of work or school, maintenance of daily work and maintenance of social life and favourable activity during the first postoperative 24 h. Additionally side effects including nausea, vomiting, allergy, and gastrointestinal adverse effects were recorded. Postoperative bleeding from the surgical site was evaluated by the surgeon for 1 h until the patients were discharged from the postoperative care unit. The degree of difficulty of extraction, mean duration of surgery, amount of local anaesthetic used and preoperative or intraoperative additional anaesthetic use were also recorded. The classification of surgical difficulty for removal of impacted mandibular third molars was determined using the difficulty index described by Pell Gregory. Patients were informed on about the Verbal Rating Scale (VRS) (0 = no pain, 5 = worst possible pain) in the preoperative proces. Postoperative pain scores were evaluated with the VRS at 15, 30 min and 1, 2, 4, 6, 12, 24 h postoperatively (the time of incision was considered the baseline). Moreover, the duration of the operation (from application of local anaesthetic agents until the end of saturation), the time of first analgesic use, patient and doctor satisfaction and side effects (nausea, vomiting, hemorrhage, vertigo and dispepsi) were also recorded.

Patients who used rescue medication recorded the exact date and time by themselves. The questionnaires were returned and then checked at a control visit one week after the second operation.

b) Statistics

Statistical analyses were performed by using SPSS for Windows (version 11.0; SPSS, Inc., Chicago, IL, USA). A sample size of 25 inviduals for each group was determined for a power of 90% at a level of 0.05.

Changes in VRS pain scores were assessed by Wilcoxon signed-rank test and the global assessments

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tested by Chi-square statistic. A value of $p<0.05$ was considered to be significant.

III. Results

The present study was carried out by a total of 75 observations in 50 patients. There were no statistically significant differences in patient age and the duration of the operation between three groups (Table 2).

No significant differences among three group were found in the degree of difficulty of extraction, mean duration of surgery, amount of local anesthetic used and preoperative or intraoperative additional anesthetic use . Again, the difference among three groups was non-significant for the effects of postoperative pain on patients' physical and social activities during first postoperative 24 h and side effects. Postoperative bleeding from the surgical site was reported in none of the patients in the three group. None of the patients in either group recorded postoperative bleeding allergy, nausea, vomiting or other gastrointestinal adverse effects associated with study medications.

Both paracetamol and lornoxicam provided adequate postoperative analgesia than placebo: patients who had pre-emptively taken either of two drugs experienced effective pain relief at all of the timelines being measured (Fig. 1).

There was only a significant difference in mean second hour VRS scores between the paracetamol and lornoxicam group in favor of lornoxicam ($p<0.05$). The overall analgesic effect of paracetamol was similar to that of lornoxicam: no statistically significant differences were found between two groups for pain intensity in the mean VRS scores at 15, 30 min and 1, 4, 6, 12, 24 h after the surgery.

Somehow we had detected a slight difference between the paracetamol and lornoxicam groups (3.54 ± 1.61 and 3.78 ± 1.14 hours respectively) regarding to the time of first rescue analgesic was taken, but it was not statistically significant ($p>0.05$). On the other hand, the same time interval was measured as 1.3 ± 1.1 hours in placebo group and which was significantly shorter ($p<0.05$) than that in the other two drug groups (Figure 2).

There were also differences among the three groups with respect to the patients satisfaction and doctor satisfaction. Statistically analysis revealed that patient satisfaction showed no significant difference between three group ($p>0.05$), furthermore the doctor satisfaction was significantly lower in the placebo group ($p<0.05$) (Table 3).

IV. Discussion

As the epidemiologic and pathophysiologic knowledge of postoperative pain improves, a new anal gesic concept has been developed and applied for the prevention of pain whereby. Analgesic treatment is started prior to trauma and surgical intervention. Within this concept, referred to as pre-emptive analgesia, it is believed that through application of an analgesic medicine or technique, pain could be either subside or be prevented before the painful stimulus. This effect is achieved by suppressing central or peripheral sensitization either together or separately. Pre-emptive analgesia gives rise to a subsiding pain pattern, a decrease in analgesic requirements, a decline in morbidity and promoting wellness to minimize length of hospital stays.[14]

The surgical extraction of impacted third molar teeth induces acute pain and thus has been used as an excellent clinical trial model for pain studies.[8,15] Studies which uses different drugs upon two extractions in the same patient (split-mouth design) for postoperative analgesia enable him or her to decrease impact of individual factors on pain severity to attain more reliable results. This study was also planned as split-mouth design, meaning to diminish individual factors likely to effect pain severity. A variety of agents have been used in preemptive analgesia for postoperative pain following third molar tooth operation.[8,16,17]

As it is reviewed from the past medical literature that there was not any study for investigating the analgesic effects of preemptively used IV paracetamol and lornoxicam in third molar surgery.

According to the study where the postoperative analgesic effects of intravenous metamizol, paracetamol and lornoxicam had been searched and compared in postoperative pain management following lumbar disc surgery, Korkmaz et al. found that pain was reduced in the metamizol and paracetamol groups, but not in the lornoxicam and control groups during a potoperative 24 h follow up period.[18]

Ong et al[15] compared the efficacy of preemptive and postoperative administration of IV 30 mg ketorolac after bilateral third molar surgery and mentioned that analgesic effect of preemptive application was significantly higher compared to placebo.

Due to the acute tissue damage, prostaglandin concentration reaches a maximum level within 3-4 hours where as the postoperative pain becomes most severe.[19] Similarly in this study, the most severe pain was experienced after 4 hours, indicated by VRS=3.6 ± 3.3 in paracetamol group and VRS=3.9 ± 3.4 in the lornoxicam group. Pektas et al,[8] also showed that the most severe pain in the diflunisal group was at the postoperative 4th hour while the most severe pain in the lornoxicam group was not experienced at the postoperative 4th but at 12th hour. Sener and coworkers[16] compared the preemptive analgesic efficacies of 4 different NSAIDs given orally, and discovered that after the usage of acetaminophen one hour prior to third molar surgery, the most severe pain started in postoperative 4th hour. Moreover, they did not detect a

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statistically significant difference between paracetamol and other NSAID groups as it is parallel to the results of our study.

In our research, there was not any significant difference in patient satisfaction between the three groups ($p>0.05$), however the doctors seemed to be less satisfied with placebo-related consequences ($p<0.05$) and thus this was statistically significant. A level of perfect satisfaction score was found in 20% of the patients in paracetamol and lornoxicam groups. In addition, good satisfaction was recorded in 60% and 68% of the patients in the paracetamol and lornoxicam groups, respectively. In contrast to the present evidence, Haglund and Von Bülzingslöwen,[20] reported that patient satisfaction was lower when paracetamol was used alone postoperatively, in comparison to rofecoxib+paracetamol combination or rofecoxib alone. On the other hand, Juhl and colleagues,[21] found that postoperative IV paracetamol increased patient satisfaction more than placebo.

In the present study, the interval of the need for a postoperative rescue analgesic in paracetamol and lornoxicam groups was 3.54 ± 1.61 and 3.78 ± 1.14 hours respectively but it was not statistically significant ($p>0.05$). On the other hand, the same period of time was detected as 1.3 ± 1.1 hours in placebo group, which was significantly shorter than the other two drug groups ($p<0.05$). Consistent with the literature, mean time of postoperative first analgesic use was 4 hours. Compatible with other studies on third molar surgery, Juhl et al[21] specified that the median duration of analgesia, as measured by the time elapsing to a request for rescue medication was significantly ($p < 0.0001$) longer after IV paracetamol 2 g (5.03 h) in comparison to IV paracetamol 1 g (3.23 h), with two significantly different active treatments ($p < 0.0001$) from placebo (1.03 h).

A study with oral rofecoxib and paracetamol used after third molar surgery showed that the durations of first analgesic use were 2.8 ± 0.5 and 3.1 ± 0.9 hours, respectively. Therefore, the differences between two groups and placebo were found out as not statistically significant.[21] The durations of first analgesic use, when ketorolac IV was used preemptively and postoperatively after third molar tooth surgery, were 8.9 and 6.9 hours respectively which was statistically significant.[15]

During the course of this study, side effects were not observed in any of these three groups and both agents specified and considered as confident and could be used safely for postoperative pain management. Juhl and colleagues,[21] compared postoperative 1 and 2 g of paracetamol with placebo and found a significant analgesic effect without any other adverse effects after third molar surgery. On the other hand, Haglund and von Bülzingslöwen,[20] reported side effects in 18.7 % of their patients. They observed side effects in 30% of their patients in the paracetamol group, including fatigue, dizziness and stomach pain in 3, 2 and 1 patients respectively.

Pektas et al. detected bleeding at the site of third molar surgery in one patient (2.5%) after the preemptive usage of 16 mg oral lornoxicam, but there was not any additional side effect that required any further treatment.[8] correspondingly, in the present research no side effects were observed in all of the three study groups.

In conclusion, this study suggests that preemptive IV paracetamol and lornoxicam are a safe and efficacious analgesic for postoperative third molar surgery compared to placebo.

Availability of injectable formulations of paracetamol and lornoxicam may be considered as an advantage for patients who cannot tolerate oral drug administration.

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Table 1 : The Pell–Gregory classification

A	The occlusal plane of the impacted tooth is at the same level as the occlusal plane of the second molar.
B	The occlusal plane of the impacted tooth is between the occlusal plane and the cervical line of the second molar.
C	The impacted tooth is below the cervical line of the second molar.
I	There is sufficient space between the ramus and the distal part of the second molar for the accommodation of the mesiodistal diameter of the third molar.
II	The space between the second molar and the ramus of the mandible is less than the mesiodistal diameter of the third molar.
III	All or most of the third molar is in the ramus of the mandible

Table 2 : Demographic properties and operation duration (mean ±SD)

	Paracetamol n=25	Lornoxicam n=25	Placebo n=25
Age (year)	24±3.8	24±3.8	22.4±3,6
Operation duration(min)	10.3±0.9	11.7±0.9	12±4,2

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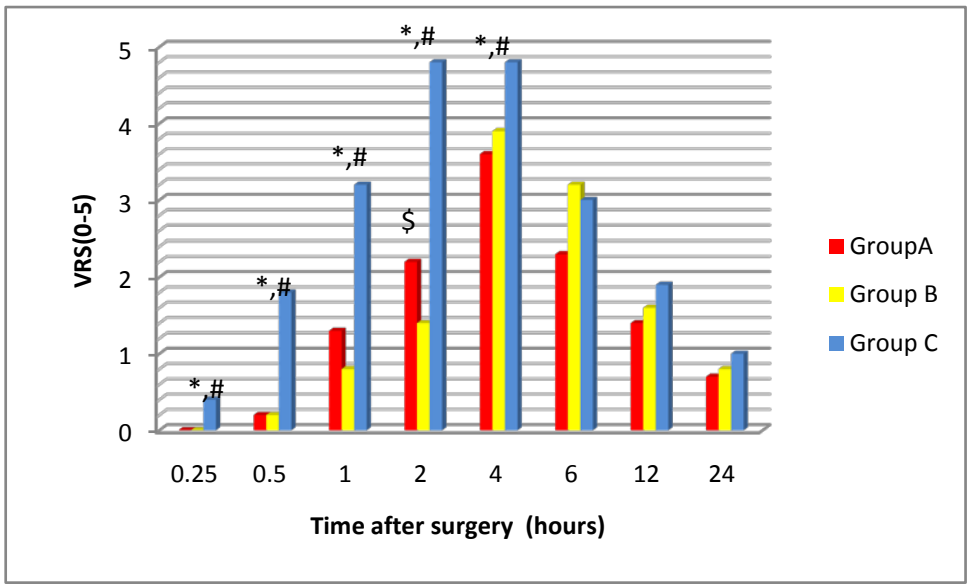
Table 3 : Doctor and patient satisfaction

	Dentist Satisfaction (n, %)			Patient Satisfaction (n, %)		
	Paracetamol (n=25)	Lornoxicam (n=25)	Placebo (n=25)	Paracetamol (n=25)	Lornoxicam (n=25)	Placebo (n=25)
Moderate	0	0	7(28%)*	5 (20%)	3 (12%)	6(24%)
Good	21 (84%)	19 (76%)	16(64%)*	15 (60%)	17 (68%)	17(68%)
Perfect	4 (16%)	6 (24%)	2(8%)*	5 (20%)	5 (20%)	2(8%)

* p<0.05:Placebo versus Paracetamol and Lornoxicam

Figure 1 : VRS score during the first 24 hours period after surgery paracetamol (Group A), lornoxicam (Group B) and placebo (Group C) groups. Values are means±SD



$ p<0.05: Group A versus Group B
*p<0.05: Group A versus Group C
# p<0.05: Group B versus Group C

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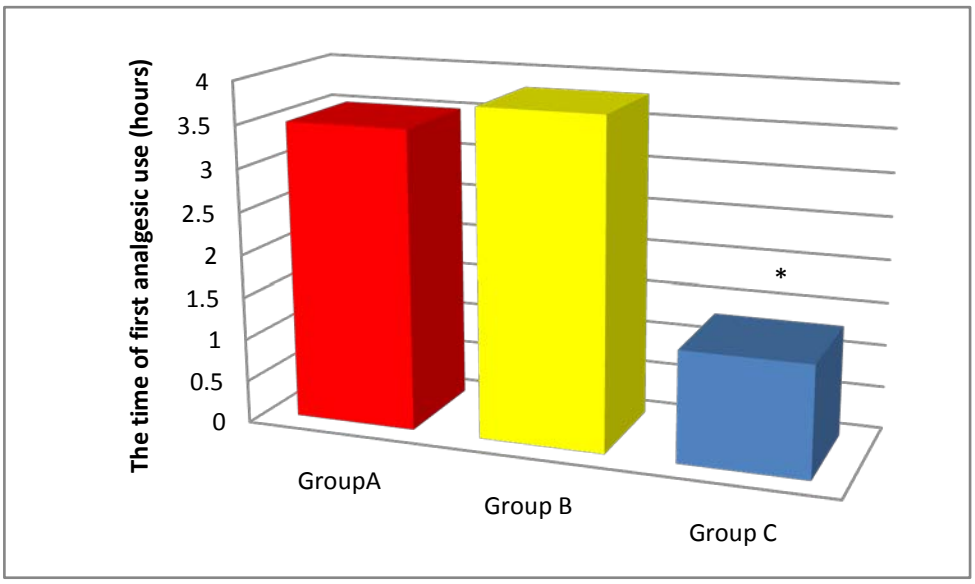
Figure 2 : The time of first analgesic use during the first 24 hours period after surgery paracetamol (Group A),lornoxicam (Group B),and placebo (Group C) groups. Values are means±SD



*p<0.05 : Group C versus Group A and Group B

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References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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