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Research Article

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Lactobacillus Species as a Potential Biomarker for Colorectal Cancer: Biopsy-Based Insights

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ABSTRACT

Colorectal cancer (CRC) is the third most prevalence type of cancer with the second mortality rate. CRC is a heterogenous disease and several factors were correlated to its development such as diet, genetics, lifestyle and recently, accumulating evidence advocate that the gut microbiota dysbiosis was an innovative and imperative player in the initiation and development of colorectal cancer. On the other hands, many recent scientific research suggested the protective role of *lactobacillus* species through different mechanisms. Such protective mechanisms ether by enhancing the immune response, suppressing the effect of free radicals, control cell cycle and proliferations and etc. To study the correlation between *Lactobacillus* and CRC among Libyan patients and wither such bactria play any role in the devolopment and progression in such cancer type This study was conducted in the city of Tripoli, Libya. The study included, ٢٠ CRC patients with colorectal cancer confirmed by colonoscopy examination and evaluated histopathologically, ٢٠ patients with large adenomas polyp and ٢٠ people with healthy colonic mucosa as control group. The sample of each patient which obtained by proximal to the colonoscopic part of the suction tube was sent to the clinical microbiology. Laboratory for isolation according to the standard laboratory procedures guideline (CSLI, ٢٠١٢). The suspected positive colonies were isolated and identified by Gram staining technique and catalase test, and further confirmed by the use of phoenix BD automated system. The results of this study revealing, significant declined of *Lactobacillus salivarius* in polypic group (٪٥) and CRC groups (٪٥) while *Lactobacillus salivarius* of the normal mucosal group represent (.(٪٣٥The *Lactobacillus rhamnosus* also shown the same pattern of *L. salivarius*. The obtained result strongly affirming the protective role of *Lactobacillus* species among Libyan CRC paients.

Key words- *Colorectal cancer; Lactobacillus; Polyp; Probiotics; Libya.*

INTRODUCTION

Colorectal cancer, is a heterogeneous disease in which malignant cells form in the tissues of the colon.[1] Colorectal cancer may be benign, or malignant. A malignant cancer can spread to other parts of the body.[2] Usually begins as a polyp, polyps may be detected endoscopically by sigmoidoscopy or colonoscopy, or radiographically.[3] Almost half of the population will develop at least one benign adenomatous colonic polyp during life, with less than 3% of those cases going on to develop colorectal cancer.[4] Unfortunately, CRC are "silent" tumors, they grow slowly and often do not produce symptoms until they reach a large size, about 60% of patients had already developed metastasis at the time of diagnosis.[5] Greater than 7595%- of colorectal cancer occurs in people with little or no genetic risk, while less than 10% of patients with CRC have a true inherited predisposition to colorectal cancer.[6] A study had been showed that hereditary colon cancer predispositions make up less than 5% of all colon cancer cases worldwide.[7] Althoght, age is a main risk factor for colorectal cancers.[8] A number of risk factors are associated with a Western lifestyle and could be considered a product of 'civilization' such as diet that is high in animal protein, saturated fats, and calories with low fibre, high alcohol consumption, having had breast, ovary, or uterine cancer, having ulcerative colitis, Crohn's disease, or irritable bowel disease (IBD), overweight and obesity, smoking and a lack of physical activity could increase colorectal cancer risk. However, the strongest contribution to environmental risk for colorectal cancer is dietary, alcohol consumption and red meat. Nevertheless, fresh fruit and vegetables and dietary fibre may be protective.[9,10] The human intestinal tract contains about 10^{14} bacteria, comprising 10^{3} species, which are crucial for food digestion, the control of intestinal epithelial homeostasis, intestinal health in general.[11] Conversely, a large body of evidence supports a relationship between those commensal bacteria development or preventions and human cancers.[12] Nowadays, its will know gut microbiome play important role in CRC initiation and progression, Gut commensal bacteria are anatomically defined as four populations: luminal commensal bacteria, mucus-resident bacteria, epithelium-resident bacteria, and lymphoid tissue-resident commensal bacteria.[13] More than 90% of the luminal commensal bacteria belong to the Phyla Firmicutes.[14] The division Firmicutes is a collection of Gram-positive,

@ Author to whom correspondence should be addressed: Dr. Salah Mohamed, Tel: ١٩٦٠٢٤٦ ٩١ ٢١٨+; E-mail: Salah.mohammed@uot.edu.ly

spore forming, obligate anaerobes and cocci or rod-shaped bacteria, including the *Enterococcaceae* and *Lactobacillaceae* families and the *Streptococcus genus; S. bovis and S. gallolyticus*. This opportunistic pathogen is normally detected in the gastrointestinal tract of about 10% of the human population.[15,16]Interestingly, the fecal carriage of *S. bovis and S. gallolyticus* was shown to be increased about 5-fold in patients with CRC and colon tumour, also it was detected up to 60% of patients with an *S. bovis/gallolyticus* endocarditis or bacteremia.[17] On the other hands, accumulating recent evidence have shown probiotics which are significant part of the gut microbiome have protective role in CRC beyond their therapeutic effect.[18] lactic acid producing bacteria (LAB) considered most predominant type, many evolving findings form clinic and laboratory experiments have shown the ability of LAB to inhibiting the initiation and progression of CRC through different mechanisms. However, probiotics considered a innovative therapeutic approach to treat IBD as safe and natural agents. For example, many studies have revealed that these bacteria play vital roles in enhancing immune responses, reducing oxidative stress, improving gut health, and maintaining genomic stability.[19,20]The diverse functions of these strains advocate their substantial character in therapeutic applications, predominantly in the of immunology, gastroenterology, and oncology. Several studies have shown that LAB play an important role in prevention of CRC, by control of apoptosis process at molecular level which is a potential and comprehensive therapeutic strategy, different studies have showed that LAB concert a role in the regulation of cell apoptosis through intrinsic and extrinsic pathways which are critical mechanisms in the prevention of CRC.[21,22] It has been shown that *Lactobacillus reuteri* (*L. reuteri*) may prevent colorectal cancer *via* downregulating nuclear factor-kappaB (NF-ϰB)-dependent gene products which regulate cell proliferation (Cox-2, cyclin D1) and survival (Bcl-2, Bcl-xL).[23] Furthermore, *L. reuteri* suppressed tumor in a dose- and time-dependent manner by suppressing necrosis factors (TNF)-induced NF-ϰB activation including NF-ϰB-dependent reporter gene which expression to slow down cancer cell growth such activities of *L. reuteri* might be involved in the extrinsic pathway of apoptosis, therefor LAB could be able to protect against CRC.[24] In addition, LAB have proven its reactive oxygen species (ROS) scavenging assets which assumed that ROS play a key role in CRC, several *in vitro* studies showed that LAB strains possess antioxidant properties and inactivate ROS *via* enzymatic mechanisms such as coupled NADH oxidase/peroxidase system and catalase.[25,26] This study aims to explore the association between *Lactobacillus* and CRC risk. By isolating and characterizing *Lactobacillus* strains from patient biopsies and comparing it with healthy, in additions to studying their antibiogram. Understanding these correlations could pave the way for novel probiotic-based interventions in CRC prevention.

MATERIALS AND METHODS

Study design

Participants and collection of biopsies

A group of 60 patients attending to Tripoli central hospital (TCH), Tripoli medical centre (TMC) and Alsafwa polyclinic in Tripoli-Libya, seeking colonoscopy procedures (Olympus Optical Co.). All biopsies were taken as a part of clinical workup and have been categorized into three groups; normal, polypic and confirmed CRC, then placed in BHI broth immediately and then transport to the microbiology lab as soon as possible. This study was conducted during 20192020-.

Isolation and identification of LAB

All tissue biopsies been homogenized under aseptic conditions for anaerobic cultivation in BHI broth for 18hr at 37ºC. A loopful of each sample was inoculated on BHI agar with 7% blood.[27] The streaked plates incubated for 24hr at 36ºC. The isolated colonies then initially been investigated to make presumptive identification of LAB. The colonies characterized by small white, mucoid, creamy, were further confirmed by Gram stain and catalase test. Identified LAB were selected for further investigations using automated system using automated BD phoenix microbiology system (PAMS, MSBD biosciences, sparks Md, USA) according to the manufacturer's instructions. The system uses panels for ID. These include the phoenix™ SMIC/ID panels intended for *in vitro* rapid ID by MIC of LAB from pure culture.

Antimicrobial susceptibility testing

The automated BD phoenix LAB antimicrobial susceptibility testing card was used to determine the susceptibility of LAB isolates to different antimicrobial agents. BD phoenix provide AST results according to CSLI criteria (CLSI, 2012) for antimicrobials as sensitive (S), intermediate (I) or resistance (R).[28]

Statistical analysis of obtained data

The data were collected and statistically analysed by using statistical package of the social science software (V22.0 SPSS). The results of all data were given in the form of rates and expressed as percentage. *Chi-square* was used to measure the associations between the variables. *P*- value that were read less than 0.05 were considered significant.

RESULTS

Isolated normal flora

Gastrointestinal tract (GIT) is inhabited with morphologically, physiologically and structurally different microorganisms; predominantly bacteria. Therefore, the analysed colorectal mucosa biopsies of 60 patients have shown a versatile bacterium such as *Escherichia coli, Klebsiella* and *Pseudomonas aeruginosa, Bacteroides oralis, Bacteroides fragilis, Staphylococcus aureus, Proteus mirabilis and Lactobacillus*. The most predominant

isolate of normal flora has been summarized (Table 1). The obtained result reveals that the polypic group exhibited the lowest microbiota percent, compared to normal and CRC groups. *E. faecalis* is a part of normal gut flora and is responsible for human disease via translocation from gut wall leading to systemic infection.[29] The results of this study shows that 29 samples have been found to contain *E. faecalis*. Notably, *E. faecalis* has the lowest prevalence in polypic group (5; 25%) compared to (8; 40%) in the CRC group. Where *E. faecalis* have prevalence in normal group by (16; 80%) (*P*-value <0.002, 95% CI, 1.00,1.3) (Figure 1). Accordingly, there was significant association between CRC and *E. faeclis*. However, data about the role of *E. faecalis* in CRC are conflicting.

The pattern of resistance among *E. faecalis* isolates of normal group was different compared with CRC and polypic group as its susceptible to Gentamycin-syn, Ampicillin, Linezodil, Ciprofloxacin, Rifapmin and Mupirocin. But its exhibited a high resistance to Teicoplanin and Vancomycin. While *E. faecalis* isolated from normal biopsies have shown intermediate resistance level on nitrofurantoin, *E. faecalis* isolated from CRC and polypic biopsies showed high resistance level this antimicrobial (Table 3).

This study demonstrated that the antimicrobial susceptibility profile for the *E. faecalis* isolates. According to the antibiogram results obtained for CRC, polypic and normal group, regarding penciiline, fluoroquinolones, aminoglycoside, macrolidis, carbapenemis and cephalosporin antibiotic classes, all *E. faecalis* isolates from different patient groups show almost the same resistance pattern, *E. faecalis* isolated from CRC and normal mucosal shown extreme resistance to both Co-trimoxazole and vancomycin, in contrary to *E. faecalis* isolated from adenomas polyp. *E. faecalis* are fundamentally resistant to many commonly used antimicrobial agents. All *Enterococci* exhibit decreased susceptibility to penicillin and ampicillin, as well as high level of resistance to most cephalosporins and all semisynthetic penicillins, ampicillin remains the treatment of choice for enterococcal infections, *Enterococci* are also intrinsically resistant to clindamycin.[30] Trimethoprim-sulfamethoxazole appears to be active against *enterococci* when tested in vitro on folate-deficient media, but fails in animal models, presumably because *Enterococci* can absorb folate from the environment.[31]

Lactobacillus species

This study was critically aimed to identify the associations of *Lactobacillus* bacterial species and CRC among Libyan patients who had colonoscopy examination. This study has shown, significant declined of *Lactobacillus salivarius* in polypic group (1; 5%) and CRC groups (1; 5%) while *L. salivarius* of the normal mucosal group represent (7; 35%). The *L. rhamnosus* also shown the same pattern of *L. salivarius*, CRC and polyps shown (0; 0%) compared to the normal group (6; 30%) (Table 2). Although *S. bovis* have been shown to have the strongest association with colorectal cancer among other species, it is not clear if SBSEC members have remarkable association or as a consequence of CRC.[32,33] This study also demonstrates that the *Lactobacillus spp* never been isolated in concurrence with any of SBSEC. The human colonic microbiota has emerged as a major environmental factor that appears to modulate the risk of colonic cancer, and dysbiosis in gut microbiota is now believed to be an underlying factor in the development and progression of CRC.[34] Regarding the other microbiota bacterial *spp*, this study shown that, the *Bacteroides fraglis and B. oralis* species have the highest prevalence in CRC group, (**17**; 85%), (19; 95%) respectively. than in the polypic, (14; 70%), (14; 70%) respectively and normal groups, (13; 65%), (15; 75%) respectively, (Table 1).

Table 1 : Distribution of isolated flora within patient's groups.

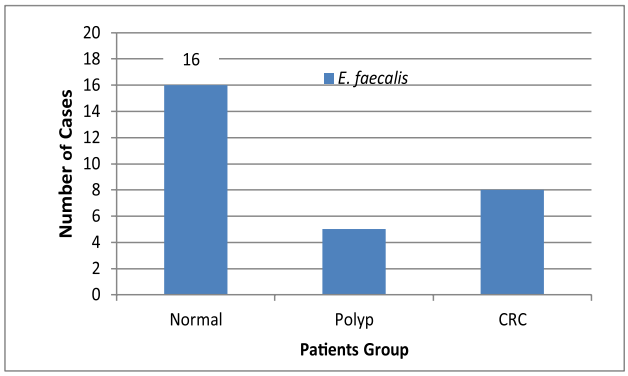
Type of bacteria	Patient's groups		
	Normal	Polypic	CRC
Escherichia coli	100%	95%	100%
Klebsiella pneumonia	20%	10%	15%
Enetrococcus raffinosus	0%	0%	15%
Klebsiella oxytoca	15%	5%	0%
Kingella denitrilcans	10%	5%	10%
Staphylococcus aureus	50%	10%	15%
Shewanella putrefaciens	5%	0%	0%
Psuedomaonase aeruginosa	15%	10%	10%
Bacteroides fragilis	65%	70%	85%
Micrococcus cassolyticus	5%	0%	0%
Bacteroides oralis	75%	70%	95%
Proteus mirabilis	30%	20%	45%
Alcaligenes faecalis	10%	5%	5%

Table 2 : Prevalence of *Lactobacillus spp* across patient's groups

Type of bacteria	Patient's groups					
	Normal group		Polypic group		CRC group	
	No.	%	No.	%	No.	%
Lactobacillus salivarius	**7**	**35**	**1**	**5**	**1**	**5**
Lactobacillus rhamnosus	**6**	**30**	**0**	**0**	**0**	**0**
***P*-value**	**<0.05**		**<0.05**		**<0.05**	

Table 3: The antibiotic susceptibility test of different antibiotics classes against *E. faeclis* isolated from different patients groups.

Antibiotics classes	Antibiotics	CRC	Polyp	Normal
Penicillins	Amoxicillin	S	S	S
	Penicilin G	S	S	S
	Oxacilline	R	R	R
	Augmantine	R	R	R
Cephalosporin	Cefuroxime	S	S	R
	Cefotaxime	I	R	I
	Cefepime	R	R	R
	Cefotraxime	R	R	R
Fluoroquinolones	Ciprofloxacin	R	R	R
Aminoglycoside	Gentamycin-syn	S	S	S
	Gentamycin	S	S	R
Macrolidis	Clindamycin	R	R	R
	Erythromycin	R	R	R
Carbapenemis	Meropenem	S	S	S
	Imipenem	R	R	R
Miscellaneous antibiotics	Daptomycin	R	R	R
	Co-trimoxazole	R	S	R
	Teicoplanin	S	S	R
	Vancomycin	R	S	R
	Chloramphenicol	S	S	S
	Linezolid	S	S	S
	Tetracycline	R	R	R
	Mupirocin	S	S	S
	Nitrofurantoin	R	R	R
	Rifapmin	R	R	S



CRC. Colorectal cancer, *x*= number of positive samples

Figure 1: Prevalence of *E. faecalis* among patients groups.

DISCUSSION

The symbiotic interactions between resident micro-organisms and the digestive tract highly contribute to maintain the gut homeostasis and many changes in the bacterial composition of the gut microbiota have been reported in colorectal cancer, suggesting a major role of dysbiosis in colorectal carcinogenesis.[35] Accordingly, the result of this study had affirmed such theory, also concluding that *Lactobacillus* species play significant role in CRC initiation and progression (P <0.05), The underlying mechanisms for their anti-cancer effects are versatile including suppression of the growth of microbiota implicated in the production of mutagens and carcinogens, alteration in carcinogen metabolism, and protection of DNA from oxide damage as well as regulation of immune system.[36]

In addition, they have been shown to change expression of different genes participating in apoptosis, invasion and metastasis, as well as cell cycle control.[3740-] Although, their anti- proliferative effects have been assessed in several cell line studies.[4143-] Further studies have shown their modulatory effects on the cancer-related signalling pathways in a cell type specific manner.[4446-] Several studies have assessed the effects of probiotics on critical steps of invasion and metastasis. Therefore, declining in the *Lactobacillus spp* that normally inhabiting gastrointestinal tract and terminating its anti-cancer effects might give the opportunity to *S. bovis*, *E. faecalis* and other types of pathogenic bacteria to colonizing the mucosa of colon and orchestrate their carcinogenic effect. However, this study also revealing there was significant association between CRC and *E. faecalis*. Nevertheless, data about the role of *E. faecalis* in CRC were contradictiry, some studies suggest a protective role or no role in CRC while others demonstrated harmful activity. For example, Viljoen, *et al*. did not find any substantial clinical association between *E. faecalis* and colon adenocarcinoma.[47] Nevertheless, a study has demonstrated that colon epithelial cells when co-cultured with *E. faecalis*, their Wnt/β-catenin signaling was activated and pluripotent transcription factors associated with differentiation were induced. subsequently, these cells were reprogrammed and transformed.[48] The anti-carcinogenic role of of *E. faecalis* has already been defined and related to their immunomodulatory.[49,50]

CONCLUSION

Many studies of modern molecular sequencing techniques have strongly demonstrate the protective role of *Lactobacillus* species in CRC. Virtually, all of the studies published in this regard have been reveals a significant association between *Lactobacillus* species and CRC. Although, this study was conducted on a group of 60 patients attending to different hospital in area of Tripoli-Libya during the years of 2019 and 2020. The biopsies have been categorized into: normal, adenomas polyps and confirmed CRC. The CRC considered the most preventable cancer and bulky number of risk factors are associated with it. Nowadays, growing evidence suggests that *Lactobacillus* species *play* important roles in the prevention of colon cancer such good bacteria such as *Lactobacillus salivarius* and *Lactobacillus rhamnosus* were significantly declined in polypic and CRC groups of compared to the normal group. Regarding *E. faecalis which* is a part of normal gut flora and is responsible for human disease via translocation from gut wall leading to systemic infection this study revealing there was significant association with CRC. *E. faeclis* co-occurred with *S.equinis* by 72.7% of *S. gallolyticus* coincident with.

What is already know on this topic

- Gut microbiome plays important role in CRC initiation and progression.

What this study adds

- *Lactobacillus* species play protective role in CRC.

Competing interests

The authors declare no competing interest.

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