Review Article

Risk of liver disease in areca nut habitual: A systematic review

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Abstract-

Background: Areca nut (AN) is one of the addictive substances known to cause deleterious effects on oral cavity as well as on various body organs including liver. But, scanty information is available reporting the adverse effects of AN chewing on the liver.

Aim: To study the risk of liver disease in AN habitual based on the relevant published data.

Methods: The literature search was performed by an electronic search of the PubMed/Medline, Scopus and Google Scholar databases using proper MESH headings and retrieved the articles published from 1998 to 2021. The eligibility criteria included: Human studies, AN habitual as study participants, use of controls and articles published in English. Data were extracted regarding characteristics of studies, characteristics of AN exposure, effect estimate and outcome of the studies.

Results: Total 253 articles were identified from various databases and 15 studies were selected that met the inclusion criteria. Among these, thirteen studies showed an association between AN habit and attenuation of risk of liver disease as determined by relative risk/odds ratio/hazard ratio. Eleven studies described additive effect of AN and HBsAg and/or Anti hepatitis C virus status on development of liver disease. However, two of the studies showed opposite results. The heterogeneity in the study designs, exposure characteristics, outcomes and confounders precluded further meta-analysis.

Conclusion: The association between AN chewing and an increased risk of developing liver disease is noted which necessitates the need for AN cessation campaign.

Keywords: Areca nut, areca nut habitual, betel quid, hepatocellular carcinoma, liver cirrhosis, liver fibrosis

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INTRODUCTION

Liver disease includes many diverse conditions that affect the morphology as well as function of the liver and accounts for approximately two million deaths/year worldwide; one million due to complications of liver cirrhosis (LC) and one million due to viral hepatitis and hepatocellular carcinoma (HCC).[1,2] The etiology of liver disease is multi-factorial. However, the growing epidemiological evidence indicates that a number of risk factors like excessive alcohol drinking, hepatitis B and C infection, obesity, family history etc., modulate

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the risk of developing chronic liver diseases.[3] Among these, areca nut (AN) consumption is also one of the risk factors. Evolutions of these risk factors provide insight into understanding of future burden of liver disease.

AN is a fruit of areca catechu palm tree, which is native of South Asia and Pacific Islands. It is chewed regularly by at least 10% of the world population of all the groups and is the fourth most widely used addictive substance.[4,5] Its consumption causes many harmful effects on the human body due to the presence of alkaloids in it.[6] These effects of the alkaloids of AN are not only limited to the oral cavity where it comes into direct contact but may also affect various organs in response to its break down and excretion products.[5] Liver is the one among them susceptible to AN induced damage.

Though a number of studies are there showing association of AN in causation of oral diseases like oral submucous fibrosis and oral squamous cell carcinoma[5-10] little evidence is available which explained the systemic adverse effects of AN. Considering this research gap in the literature, the present review was carried out to address a question "Are AN habitual at increased risk of developing liver disease" The Hypothesis would be, the AN habitual may be at increased risk of developing liver disease. To our knowledge scanty literature is available reporting the detrimental effects of AN chewing on liver.

METHODS

Search protocol (data source and search strategy)

The first step of search strategy comprised a search of Medline, PubMed databases of the National Library of Medicine, National Institutes of Health, Bethesda, Maryland for appropriate articles addressing the focused question. Databases were searched from 1998 up to and including 2021 using various combinations of the following keywords: "AN," "betel nut," "areca catechu," "AN habitual," "betel nut habitual," "betel nut chewing," "liver fibrosis," "fibrosis of liver," "LC," "cirrhosis of liver," "liver disease," "hepatic disease" "HCC," "liver cancer," "hepatoma" etc., and the second step was to hand-search the reference lists of original and review articles that were found to be relevant in the first step.

Titles and abstracts of articles obtained using the above-described search protocol were screened by each author. Only full text articles were selected after assessing its eligibility and checked for agreement. Any disagreements between the authors were resolved via discussion. All the well-designed original studies published in English that covered the effect of AN consumption on liver were selected. Search strategy used in PubMed was as under.

([[[[areca* [Title/Abstract]] odds ratio [OR] catechu* [Title/Abstract])] OR "betel nut*" [Title/Abstract]] OR "Areca" [Mesh]) AND ([[[[[[[[[[[[[[LC"[Title/Abstract]] OR "LC"[Title/Abstract]] OR "cirrhosis of liver" [Title/Abstract]] OR "hepatic disease" [Title/Abstract]] OR "fibrosis of liver" [Title/Abstract]] OR "hepatic disease*" [Title/Abstract]] OR "HCC *" [Title/Abstract]] OR "liver cancer" [Title/Abstract]] OR "HCC *" [Title/Abstract]] OR HCC [Title/Abstract]] OR "hepatoma*" [Title/Abstract]] OR "Carcinoma, Hepatocellular" [Mesh]) OR "liver carcinoma" [Title/Abstract]) OR "Liver Diseases" [Mesh]).

Inclusion and exclusion criteria

With the consensus of all the authors the following eligibility criteria were decided for the selection of articles. (1) human studies; (2) test group: Individuals consuming AN, (3) control group: individuals not using AN in any form, (4) individuals suffering from liver disease and (5) articles published in English. All prospective, retrospective, case–control, community-based, hospital-based studies were included in which association between AN consumption and liver disease is assessed. Studies on animal models, unpublished articles, letters to the editor, review articles, books were excluded. Habitual having a habit of chewing AN with or without tobacco associated with alcohol consumption were excluded.

From the enrolled studies, data was extracted regarding characteristics of studies, study population, characteristics of exposure, assessment tools used to evaluate AN habit and liver disease as well as effect estimate and outcome of the studies. We had planned to undertake meta-analysis but due to heterogeneity in studies with reference to type of population, type of exposure, type of assessment methods used, we did not undertake meta-analysis that would have provided a summary estimation of different results.

RESULTS

In total, 253 articles were retrieved from electronic-database (PubMed/Medline: 51, SCOPUS: 42, Google Scholar: 125 and EMBASE: 19 and manual searching: 16). Out of these, 207 titles remained for screening after the removal of duplicates. On review of the titles and abstracts of all these articles, 179 publications were excluded because these did not report association of AN in development of liver disease. Consequently, 28 full-text articles were then reviewed to assess their eligibility,

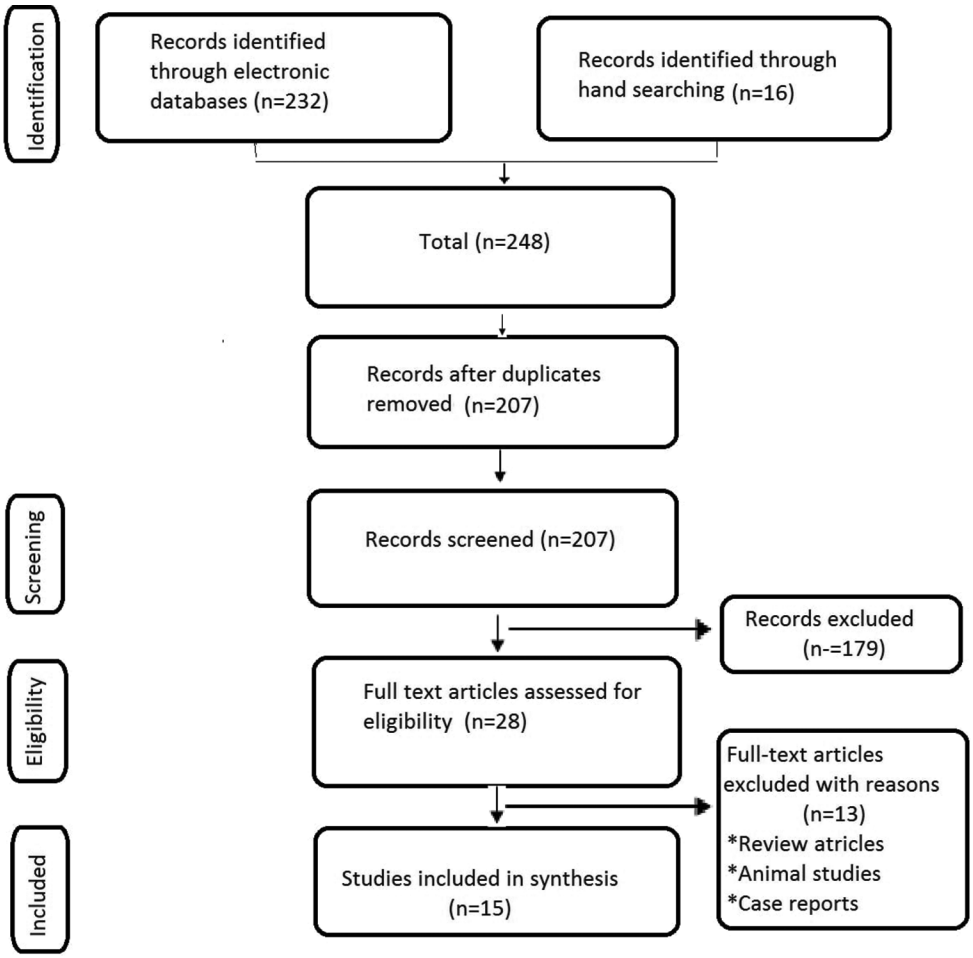

Figure 1: "Preferred reporting items for systematic reviews and meta-analyses" flow-chart showing flow of information

out of which, 13 were excluded because these were review articles, case reports or articles with animal studies. Ultimately, 15 articles that met the eligibility criteria were included and processed for data extraction to include in this systematic literature review. Figure 1 depicts 'Preferred reporting items for systematic reviews and meta-analyses' flow-chart showing flow of information.

Characteristics of the studies and study subjects

All the studies included in the present review were human studies conducted either at hospital or in community [Table 1].[11-25] Out of these, eight were case–control studies,[11,12-14,16-18,21] four were community-based studies,[15,19,20,25] one study each was prospective, retrospective and population-based cohort study.[22-24] About geographical location of the studies, twelve studies were conducted in Taiwan, two in India and one in Pakistan. These three countries are located in Asia, but Taiwan in East Asia while India and Pakistan in South Asia. The sample size ranged from 26 to 60,326 participants. All the enrolled studies included control or comparison group except a study by Wang LY *et al.* 2003.[19] as shown in Table 1.

Characteristics of study subjects revealed that the age of the participants ranged from 14 years and above. In a study by Tsai JF *et al.*,[13] the participants were in wider age range, which was from 23 to 83 years. In terms of gender of study population, eligible subjects consisted of male and female, except for two studies that recruited either male or female.[19,24] With reference to type of liver disease, in four studies, HCC;[13,17,19,25] in five studies, LC;[12,16,20,22,23] in one study each, liver fibrosis and chronic liver disease were the AN associated disorder.[11,18] In a study by Tsai JF *et al.*,[14] all HCC patients with habitual betel quid chewing also had LC while Wu GHM *et al.*[15] assessed association of betel quid chewing with LC as well as HCC. In two studies, researchers did not mention about the type of liver disease [Table 1].[21,24]

Assessment tools used to evaluate AN habit and liver disease

To get detail information relevant to AN habit from participants, "standardize personal interview using a structured questionnaire," was the assessment tool used in most of the studies.[12-19,23] In a study by Chu YH *et al.*[22]

retrospectively analyzed data was retrieved from Adult Preventive Medical Services and the National Health Insurance Research Datasets and habit information was gathered from the questionnaire. In three studies, information about exposure to AN was obtained through history[11,21,24] and personally interviewing the participants.[25] Lin CF *et al*. invited the participants to participate in physical examination and detailed questionnaire about health history to collect the information relevant to AN habit.[20] To evaluate the type of liver disease, cytology and biopsy of liver,[13,14,16-18] ultrasonography abdomen[11,12,13,20,25] and biochemical markers for liver diseases like aspartate aminotransferase (AST), alanine aminotransferase, alkaline phosphatase (ALP) etc.[12,15,18-22,24,25] were the assessment tools used in the enrolled studies.

Characteristics of exposure

The daily consumption of AN ranged from one quid a day to 28 times daily and duration of AN consumption ranged from 6 months to >30 years in the included studies. Three studies didn't state about the frequency[11,23,25] while six studies didn't mention the duration of AN consumption [Table 1].[11,19,20,22,24,25] Nonetheless the terms, "Never," "Occasional" and "Frequent" are used to describe the frequency of AN consumption in two studies.[22,24] Similarly, to describe the duration of habit, "Never chewer," "Current chewer" and "Ex chewer" are the words used.[15,18] With reference to duration, Lan TY *et al*. categorized the participants as never chewer and ever chewer [Table 2].[23]

As shown in Table 2, in regards to the form of AN consumed, seven studies mentioned consumption of AN in the form of BQ[12,17-20,23,25] while in three studies it was consumed either as AN with betel leaf or AN with betel fruit or mixed form.[13,14,16] In a study by Singroha K *et al*. the consumption was in the form of AN with tobacco called as "AN quid."[21] However, in three studies, participants consumed AN or BN only.[11,22,24] In one of the studies by Wu GH *et al*. the type of betel-chew used was "Lao-Hwa."[15] "Lao-Hwa" is used in Keelung city and is prepared by combining pieces of unripe A. catechu palm nuts with a piece of the inflorescence (flower head) of the Piper betel vine and red lime paste, that is swallowed after chewing.[26] However, in another study, form of AN was not mentioned [Table 2].[25]

Effect estimates or outcome-AN as an independent risk factor for liver disease

Among all the included studies, twelve studies observed AN as an independent risk factor for various liver diseases like LC,[12,15,16,20,22,23] HCC,[13,15,17,19] HCC complicating cirrhosis,[14] liver fibrosis,[11] chronic liver disease [Table 3].[18] The population-attributable risk for BQ chewing was 20.19% in HCC,[13] 11.60% in LC[16] and 20.10% in HCC complicating LC.[14] Wang LY *et al*. studied the risk of HCC in three habits of substance use (smoking, alcohol drinking) including BQ habit and observed (relative risk [RR] = 1.59 (95% confidence interval [CI]: 0.89–2.85) in BQ chewers among these three habits of substance use.[19] On estimation of serum biomarkers to assess the independent role of AN habit in causation of liver disease, six studies

Table 1: Characteristics of all included studies including type of liver disease

Author	Year	Study design and duration of study	Study region	Study/control participants	Age range (years)	Type of Liver Disease
Tsai *et al*.[13]	2001	Case-control study 1996-1997	Taiwan	263/263	23-83 median age 59 years	HCC
Lin *et al*.[18]	2002	Hospital-based case-control study 2000-2001	Taiwan	79/107	20-74	CLD
Wang *et al*.[19]	2003	Prospective community-based cohort study	Taiwan	11837 males/not available	30-64	HCC
Tsai *et al*.[16]	2003	Case-control study 1996-1997	Taiwan	210/210	40-69	LC
Sun *et al*.[25]	2003	Community-based prospective study	Taiwan	112 HCC cases	30-64	HCC
Tsai *et al*.[14]	2004	Case-control study	Taiwan	210/210	40-69	HCC complicating cirrhosis
Hsiao *et al*. [12]	2007	Community-based case-control study 1997-1999	Taiwan	42/165	Above 20 Mean age 50.2±14.0	LC
Lan *et al*.[23]	2007	Prospective Population-based cohort study 1989-1996	Taiwan	60326/5602	50-66 years	LC patients 571
Wu *et al*.[15]	2009	Community-based integrated teaching program 1999-2003	Taiwan	60326/56483	30-79 years	LC and HCC
Lin *et al*.[20]	2008	Prospective Community-based study	Taiwan	2063/947	41-60	LC
Jeng *et al*.[17]	2014	Hospital-based case-control study 2004-2005	Taiwan	200/200	41-72	HCC
Saawarn *et al*.[11]	2016	Case-control pilot 2015	India	21/5	14-45	LF
Fatima and Sultana[24]	2016	Prospective	Pakistan	BN chewer 15/10	30-38	Not mentioned
Singroha and Kamath[21]	2016	Case-control study	India	30/10	21-80	No disease
Chu *et al*.[22]	2018	Retrospective	Taiwan	4133/106113	40 and above	LC

HCC: Hepatocellular carcinoma, LC: Liver cirrhosis, LF: Liver fibrosis

Table 2: The characteristics of areca nut exposure in all included studies

Study ID	Frequency of use of AN range	Duration of AN use range	Type or form of AN
Tsai *et al*. (2001)[13]	16–25 quids/day	<20–>30	AN with betel leaf or AN with betel fruit or mixed
Lin *et al*. (2002)[18]	>1 quid/day	Never chewer Current chewer Ex-chewer	BQ
Wang *et al*. (2003)[19]	1–10 quids/day >10 quids/day	Not available	BQ
Tsai *et al*. (2003)[16]	18–28 quids/day	<20–>30	AN with betel leaf or AN with betel fruit or mixed
Sun *et al*. (2003)[25]	Not available	Not available	BQ
Tsai *et al*. (2004)[14]	>200/weekly	<20–>30	AN with betel leaf or AN with betel fruit or mixed
Hsiao *et al*. (2007)[12]	51.4 quids year >55 quid years ≤55 quid years	>25 years	BQ
Lan *et al*. (2007)[23]	Not available	25–40 years	BQ
Wu *et al*. (2009)[15]	≤5 betel portions/day >20 portions/day	<10–≥20 Never chewer Ex-chewer current chewer	Lao-Hwa - Combination of unripe AN with piece of influorescence and lime paste
Lin *et al*. (2008)[20]	>1 quid per day	Not available	BQ
Jeng *et al*. (2014)[17]	>1 per day	>1 year	BQ
Saawarn *et al*. (2016)[11]	Not available	Not available	AN Chewer
Fatima T, Sultana V. (2016)[24]	Neveroccasional frequent	Not available	BN
Singroha and Kamath (2016)[21]	2–8 times/day	6 months–30 years	AN with tobacco AN quid
Chu YH *et al*. (2018)[22]	Neveroccasional frequent	Not available	BN

AN: Areca nut, BQ: Betel quid, BN: Betel nut

showed positive association.[12,14,18-20,22] But, one of the studies showed opposite results as serum glutamic oxaloacetic transaminase level was significantly high in nonbetel nut chewers groups (24.7 ± 6.40) as compared to chewers group (17.5 ± 5.72).[24] In another study, authors concluded that long-term chewing of AN is not hepatotoxic because though there was statistically significant difference between betel nut chewers (mean = 33.80) and nonchewers (mean = 24.20), the levels of AST as well as ALP were within normal range [Table 3].[21]

Regarding duration of consumption of AN, three studies reported increased risk of liver disease with odds ratio [OR] = 15.06 (95% CI, 4.36–39.09) for HCC,[13] OR = 9.04 (95% CI, 1.13–67.21) for LC[16] and OR = 18.89 (95% CI, 2.58–92.44) for HCC complicating LC,[14] if the duration of consumption is >30 years. Likewise, risk of liver disease was reported to be more in current chewer (OR = 3.9, 95% CI, 1.6–10.1 and hazard ratio [HR] = 3.87, 95% CI, 2.62–5.73), ever chewer HR = 1.62 (95% CI, 0.79–3.31) and frequent chewer OR = 3.06 (95% C. I: 1.69–5.57) as compared to ex-chewer, never chewer and occasional chewer, respectively.[15,18,22,23] One of studies by Wu GH *et al*. showed controversial results relevant to duration of habit, as the risk of liver disease being maximum on consumption of AN for 10–19 years (HR = 5.69, 95% CI, 3.21–10.08) as compared to duration >20 years (HR = 1.98, 95% CI, 1.18–3.32) [Table 3].[15]

Similarly, concerning the association of risk of liver disease with amount of AN consumed, five studies showed increased risk of HCC and LC with increase in amount of BQ consumed [Table 3].[12,13,15,16,19] However, one study mentioned contradictory results, as HCC complicating cirrhosis risk was maximum on consumption of 100–200 quids ×1000 (OR = 12.59, 95% CI, 2.78–49.11) while the same study showed reduced risk of liver disease on consumption of >200 quids ×1000 (OR = 7.13, 95% CI, 1.92–22.73).[14] In a study by Hsiao TJ *et al*. more risk of LC is reported on consumption of BQ >55 quid/year.[12]

As regards to the form of AN consumed, two studies showed maximum risk of liver disease on consumption of AN with Betel leaf (OR = 5.93, 95% CI, 1.87–16.65 and OR = 7.55, 95% CI, 2.42–20.18).[14,16] One of the studies showed maximum risk of HCC on consumption of AN with betel fruit (OR = 5.02, 95% CI, 2.25–11.50).[13] Nevertheless the minimum risk of LC, HCC and HCC complicating LC was noted on consumption of mixed form of AN in these studies [Table 3].[13,14,16]

Additive or combined effect between AN and HBsAg and/or Anti hepatitis C virus status [Table 3]

Though AN is observed to be an independent risk factor for development of liver diseases, eleven enrolled studies described combined or additive effect between AN and HBsAg and/or Anti hepatitis C virus status.[12-20,22,25] The estimated risk for HCC, LC and HCC complicating LC were found to be higher in betel quid chewers infected with hepatitis B virus (HBV) or hepatitis C virus infection in these studies [Table 1]. However, the highest risk is noted for HCC by additive interaction between HBV infection and BQ chewing with OR = 81.00 (95% CI, 18.02–204.13).[14] Similar increased risk is observed for

Table 3: Effect estimate of areca nut chewing with reference to the type, duration and amount of areca nut chewed

Study ID	Effect Estimate	Conclusion of study
Tsai *et al*. (2001)[13]	Independent risk of BQ chewing in HCC (OR=4.05, 95% CI, 2.35–7.00) Estimated population attributable risk BQ chewing 20.19% (95% CI, 9.81–23.78) Risk of HCC based on type of BQ ingredients Maximum risk: Areca-nut with betel fruit OR=5.02 (95% CI, 2.25–11.50) Risk of HCC based on duration of BQ consumed Maximum risk: >30 times OR=15.06 (95% CI, 4.36–39.09) Risk of HCC based on total amount of BQ consumed (quids×1000) High risk: >299 OR=8.78 (95% CI, 1.87–34.01)	Risk of HCC increased as duration and amount of BQ chewing increased
Lin *et al*. (2002)[18]	CLD risk due to Habitual BQ chewing Never chewer OR=1.0 (95% CI) Ex-chewer-OR=2.0 (95% CI, 0.7–5.7) Current chewer OR=3.9 (95% CI, 1.6–10.1) Multivariate-adjusted ORs were 4.7 (95% CI, 1.3–16.8) and 7.9 (95% CI, 2.1–30.4) for subjects with 1–2 and 3 habits, respectively, compared to subjects with no habit	Increasing linear trend in CLD risk is noted
Wang *et al*. (2003)[19]	BQ chewers RR=1.59 (95% CI: 0.89–2.85) among three habits of substance use RR based on Quantity of BQ chewed per day Nonchewers RR=1.00 1–10 RR=1.44 (95% CI, 0.66–3.14) >10 RR=1.92 (95% CI, 0.87–4.22)	Habitual BQ chewing is associated with an increased risk of HCC
Tsai *et al*. (2003)[16]	Risk for Cirrhosis in BN chewing OR 5.94 (95% CI, 3.01–11.79) The estimated population-attributable risks for BQ chewers was 11.60% Type of BQ ingredients–Maximum risk in AN with betel leaf OR=5.93 (95% CI, 1.87–16.65) Duration of chewing-maximum risk if duration >30 years OR=9.04 (95% CI, 1.13–67.21) Total amount consumed (quids×1000) >200 OR=6.40 (95% CI, 1.73–20.82)	BQ chewing appears to be an independent risk factor for cirrhosis
Sun *et al*. (2003)[25]	Risk for HCC in BQ chewing RR=0.7 (95% CI, 0.4–1.3) Joint effect of HCV infection and lifestyle habits on the risk of HCC is reported	There is an additive interactive effect in causation of HCC
Tsai *et al*. (2004)[14]	Population-attributable risk was 20.10% for BQchewers BQ OR=5.94 (95% CI, 3.01–11.79) Type of BQ ingredients maximum risk: ANwith betel leaf OR=7.55 (95% CI, 2.42–20.18) Duration of chewing maximum risk: >30 years OR=18.89 (95% CI, 2.58–92.44) Total amount consumed (quids×1,000) maximum risk 100–200 quids OR=12.59 (95% CI, 2.78–49.11)	There is an additive interaction between BQ chewing and chronic hepatitis B and/or hepatitis C virus infection
Hsiao *et al*. (2007)[12]	Combined effect of other risk factors with BQ on the development of LC HBsAg positive+>55 quids/year OR=4.8 (95% CI, 1.2–19.3) Cigarette smoking >5 pack-year s+>55 quids/year OR=5.2 (95% CI, 1.8–14.8) Alcohol drinking + >55 quids/year OR=7.7 (95% CI, 2.3–25.8)	BQ chewing in combination with other risk factors is more harmful
Lan *et al*. (2007)[23]	HR by liver cirrhosis and BQ chewing status Never chewer HR=1.00 Ever chewer HR=1.62 (95% CI, 0.79–3.31)	The effects of BQ chewing on mortality from all causes may be cumulative
Wu *et al*. (2009)[15]	Adjusted HR for associations between exposure to betel chewing and LC/HCC: Current chewer HR=3.87 (95% CI, 2.62–5.73) Quantity of betel chewed (portions/d), Nil if >20 portions/dHR=4.83 (2.54–9.18) Duration of betel chewing (years) 10–19 HR=5.69 (95% CI, 3.21–10.08) Cumulative exposure to betel chewing (portion-days) If >8.8×104 HR=3.94 (95% CI, 2.35–6.62) Age betel first chewed (years) If 20–29 years HR=3.71 (95% CI, 2.24–6.14)	Increased risks of LC and HCC were found in betel chewers
Lin *et al*. (2008)[20]	ALT-OR=1.5 (95% CI, 1.1–1.8) AST OR=1.3 (95% CI, 1.1–1.7) GGT OR=0.7 (95% CI 0.5–1.1) BQ chewing was independently associated with risk of LC diagnosed by USG with an adjusted OR of 1.7 (95% CI, 1.2–2.3)	BQ chewers were associated with biochemical dysfunction and LC
Jeng *et al*. (2014)[17]	Habitual BQ chewing OR=4.95 (95% CI, 2.54–9.65) was associated with HCC Significant hepatic fibrosis was noted between 45.8% and 91.7% of patients with BQ chewing	Adverse hepatic fibrosis play important role in the pathogenesis of BQ related HCC
Saawarn *et al*. (2016)[11]	19% of total study subjects and none in control showed fibrotic changes in liver on USG Out of which 75% were OSMF patients and 25% were AN chewers without OSMF	Ill effects of AN chewing may be evident in liver even before it involves the oral mucosa
Fatima and Sultana (2016)[24]	SGOT level was significantly high in non-BN chewers groups (24.7±6.40) as Compared to chewers group (17.5±5.72) Bilirubin (total and direct) and alkaline phosphate was within normal range	Controversial observations are reported
Singroha and Kamath (2016)[21]	Statistically significant association (P=0.031) was observed between the control (mean=24.20) and cases (mean=33.80) for AST Statistically significant association (P=0.02, P<0.05) was observed for ALP between control (mean=108) and cases (mean=155.38). The levels of ALT remained unaltered	Long-term chewing of AN is not hepatotoxic

Contd...

Table 3: Contd...

Study ID	Effect Estimate	Conclusion of study
Chu *et al*. (2018)[22]	There were significant relationships between cirrhosis and BN in both males and females (P<0.0001) The risk of cirrhosis was greater in females than males Females with LC-OR in occasional chewer OR=2.91 (95% CI: 1.75–4.83) and frequent chewers OR=3.06 (95% CI: 1.69-5.57) LC in males-OR in occasional chewers OR=1.76 (95% CI: 1.47–2.10) and frequent chewers OR=2.32 (95% CI: 1.90-2.85)	Significant relationships between BN chewing and cirrhosis in both male and female nonalcohol drinkers is reported

USG: Ultrasonography, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, BQ: Betel quid, BN: Betel nut, SGOT: Serum lutamic-oxaloacetic transaminase, HBsAg: Hepatitis B surface antigen, HCV: Hepatitis C virus, HBV: Hepatitis B virus, CLD: Chronic liver disease, OR: Odds ratio, CI: Confidence interval, RR: Relative risk, HR: Hazard ratio, AN: Areca nut, HCC: Hepatocellular carcinoma, LC: Liver cirrhosis, OSMF: Oral submucous fibrosis, GGT: Gamma- glutamyl transferase

combined effect of HBsAg positivity with BQ chewing in ever chewers and current or ex chewers.[15,18,19,25] The combined effect of anti-hepatitis C virus positivity with BQ chewing also depicted more risk in ever chewers[18,19] and current or ex chewers.[15,25] In a study by Sun CA *et al*., on evaluation of joint effect of hepatitis C virus infection and lifestyle habits (anti-hepatitis C virus positive + habit) on the risk of HCC, RR was found to be maximum for BQ (RR = 6.8, 95% CI: 1.7, 28.2) as compared to smokers (RR = 3.9, 95% CI: 2.0, 7.7) and drinkers (RR = 4.1, 95% CI: 1.3, 13.0).[25] Likewise, the risk for LC in HBsAg positive status with BQ chewing, cigarette smoking >5 pack-years with BQ chewing and alcohol drinking with BQ chewing more than 55quids/year was OR = 4.8 (95% CI, 1.2–19.3), OR = 5.2 (95% CI, 1.8–14.8) and OR = 7.7 (95% CI, 2.3–25.8), respectively, which was found to be greater than the individuals consuming the amount <55 quids/year. In addition to these, four studies reported, alcohol drinking, cigarette smoking, betel quid chewing, were also associated with a significantly elevated risk of chronic liver disease [Table 3].[12,18,19,25]

DISCUSSION

The present review addresses the effect of AN consumption on risk of liver disease. On the basis of the literature reviewed, authors found it difficult to document the individualistic effect of AN on liver as AN is often consumed in combination with other components. Nevertheless, whatever may be the form, AN is the main ingredient by weight in all types of AN preparations and thus, authors took this opportunity to include the studies describing population data for consuming all the forms of AN as a valid reference value.[27,28]

In this review, 15 articles met the eligibility criteria out of 253 retrieved articles. Among all these enrolled fifteen studies, the outcome of thirteen studies revealed association of AN in development of liver disease. Among these, twelve were from Taiwan suggesting more prevalence of the adverse effects of AN on liver in Taiwan, for which reasons might be; (i) the form of AN consumed, (ii) larger amount and longer duration of AN consumption, (iii) combined effect of AN and viral infection, as hepatitis A and/or B infection is quite common in Taiwan.[13,14,16] However, two studies, one from India and other from Pakistan showed no association between AN habit and liver disease.[21,24]

It is a well-established fact that the form or method of AN consumption vary from country to country. In Taiwan, the betel quid generally contains AN, lime, a piece of P. betel inflorescence containing safrole, with or without P. betel leaf. AN is often used in the unripe stage when it is green, like a small olive and without tobacco in Taiwan whilst in India, AN is usually consumed along with tobacco.[28,29] In Eastern India and southern Sri Lanka, fermented AN is popular. It is stated that powdered AN if placed in the oral cavity results in rapid appearance of arecoline in blood plasma, indicating speedy systemic absorption.[30] No matter what is the form, AN consumption is unsafe for oral and general health. The commercially manufactured stored forms of AN like "Ghutka," "Pan masala" are more harmful.[28,31]

Eight studies reported increased risk of liver disease with increase in duration and/or amount of consumption of AN.[12-16,19,22,23] A maximum risk is reported on consumption for more than 30 years in a study by Tsai JF *et al*. (OR = 18.89, 95% CI, 2.58–92.44.[14] With reference to the amount of AN consumption, maximum risk for liver disease (HCC) was reported on consumption of >299 quid ×1000 (OD = 0.78, 95% CI, 1.87–34.01).[1] Likewise, the studies reported increased risk of liver disease in current chewers and ever chewers as compared to ex-chewers and never chewer, respectively.[15,18,23]

Wang LY *et al*. noticed significant dose–response relationship between the risk of HCC and the number of habits of substance use.[19] Risk increases with the increase in number of habits as reported in two studies which may be due to combined effect of different substances.[18,19]

Wu GHM *et al.* confirmed independent dose– response relationships of betel chewing with increased risk for either LC or HCC.[15] With reference to age they reported that the betel-related risk of LC is larger in under-50s, while the risk of betel-related primary HCC is larger in over-50s.[15]

Similarly, Sawaan *et al.* mentioned that the prolonged AN chewing can cause fibrotic changes in liver even before the appearance of oral abnormalities like submucous fibrosis, as they found fibrotic changes in 12.5% of the AN chewer and 23% of oral submucous fibrosis patients.[11] Also, they stated that the severity of fibrotic changes in liver was proportional to the severity of oral submucous fibrosis.[11] However, in contrast to this, Singroha K. *et al.* concluded that even long term AN consumption may not be hepatotoxic in isolation, rather acts as an associative agent in the presence of a preexisting condition such as hepatitis.[21] Still, it is curious and crucial to understand why long term AN chewing is linked with liver disease. Though there are multiple mechanisms documented in the literature, main culprit is the alkaloids present in AN (four main alkaloids namely arecoline, arecaidine, guvacoline and guvacine).

Based on available literature, various reasons explaining the role of AN in causation of liver disease are as under.[11,12-14,16]

1. An exposure of fibroblasts to the extracts of betel has been suggested to trigger collagen synthesis and stabilize collagen fibrils. 2. A significant amount of reactive oxygen species production is induced by AN extract. 3. Evidence of oxidative reactions is associated with fibrogenesis occurring in the liver, 4. Fibrotic liver injury results in activation of the hepatic stellate cell which undergoes a phenotypic change to a proliferative myofibroblast-like cell that synthesizes excess interstitial collagens and other matrix components.

In addition to this, copper content in AN stimulates lysyl oxidase enzyme which enhances cross-linkage of collagen and elastin fibers that causes fibrosis of submucosal tissues[32] Also AN increase the risk of toxic hepatitis by modulating the function of hepatic detoxification system.[33,34] One of the ingredients of Taiwanese betel quid preparation, safrole may be responsible for hepatocarcinogenesis as safrole-DNA adducts were found in HCC tissue from a heavy betel quid chewer.[35,36] Bleibel W and Saleem suggested nonalcoholic steatohepatitis as the underlying cause of liver disease in betel chewers.[37]

One of the reasons for liver damage in AN habitual is ingestion of Aflatoxin B1 infected AN, as Aflatoxin B1 is a known hepatotoxin.[38,39] Yan Liu and Felicia Wu reported that aflatoxin may play a causative role in 4.6%–28.2% of all global HCC cases.[40] Aflatoxin exposure in food is a significant risk factor for HCC.[41] However, Aflatoxin has a synergistic effect with hepatitis B and C virus in causing liver cancer.[42,43] Ten included studies reported that the combined effect of AN and viral hepatitis on liver is more severe than AN alone. Related to this, two ways causal relationships can be thought off. (i) AN consumption reported to immunologically suppress body defense and increase the risk of toxic hepatitis, which might be related to other reactive oxygen adducts formed as a result of habitual betel chewing. On the contradictory, chronic hepatitis B and C virus infection compromises the immunity, makes an individual more susceptible to action of AN.

Before concluding, authors consider to describe few limitations of the present systematic review as (i) the low number of studies retrieved, the use of a language filter (which restricted our search to English language articles only), (ii) maximum studies from same geographical location (12 out of 15 studies from Taiwan), the results might not be well applicable to other populations. However, authors wish to undertake meta-analysis by including a greater number of studies, by including the studies from different locations where the AN habit is rampant. Likewise, similar studies should be carried out at other places or countries including India, as India is the second largest producer of AN producing 330,000 million tons of AN per year as well as viral hepatitis is a cause for major health care burden in Indian population.[28,44,45]

Last but not the least, Increased attention on the development of AN cessation programs is long overdue. A recent Indian study by Singh PK *et al.*[46] stated that unlike tobacco, no global policy exists for the regulation and control of AN consumption and its cessation. There is should a policy intervention to prevent both new generations from taking up AN consumption habit and helping current users to give up the habit. In addition, research is needed to examine the intention to quit among AN users, separately for all three categories–those who consume AN with tobacco, without tobacco and those who consume in both the forms – to develop an appropriate quit.[46,47] With reference to the similar issue, Paulino YC, *et al.*[48] (2020) offers a notable innovations, "Betel Nut Intervention Trial" which is a randomized controlled cessation trial designed to test the efficacy of an intensive AN/BQ cessation program.

CONCLUSION

It is apparent from this systematic review that most of the studies provide evidence supporting the increased

risk of liver disease in AN habitual though the studies with controversial results also exist. As the prevalence of consumption of AN is increasing day by day, the population should be made aware about the health issues related to it, as the health of consumers is at stake.

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Conflicts of interest

There are no conflicts of interest.

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